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PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Steroids and their Production

We, N. V. PHILIP'S GLOEILAMPENFABRIEKEN, a limited liability Company, organized and established under the laws of the Kingdom of the Netherlands, of Emmasingel 29, Eindhoven, Holland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

Steroids which differ from one another with respect to the nature and position of the substituents attached to the various carbon atoms of the cyclopentanoperhydrophenanthrene skeleton are known in large numbers. Many of these compounds have become known by their interesting pharmocological properties. Mention may, for example, be made of steroids having hormonal activity, for example steroids from the oestrone, androstane and pregnane series. The hormones of the first-mentioned series have a steroid skeleton with an aromatised A and/or B ring, a hydroxy group in the 3-position and a keto- or hydroxy group in the 17-position. The 17-keto group may be converted into a 17-hydroxy-17-ethinylide. As a rule, the hormones of this series influence, specifically female functions of mammals. The hormones from the androstane series have no aromatized rings in the steroid skeleton, but they have a keto- or a hydroxyl group in the 3-position, frequently a double bond between the carbon atoms 4 and 5 or 5 and 6 and as a rule a hydroxy- or a keto group in the 17-position. Furthermore these compounds have a methyl group in the positions 10 and 13. The hormones from this series as a rule have a strong influence on specifically male functions of mammals. The hormones from the pregnane series may have a group —CO—CH_2OH, —CHOH—CH_2OH, —CO—CH_3, or —CHOH—CH_3, and in some case a hydroxy group also in the 17-position of the steroid skeleton, furthermore frequently a keto- or hydroxy group in the positions 3 and/or 11 and in some cases a double bond between the carbon atoms 4 and 5. A methyl group is always attached to the carbon atoms 10 and 13. Many of these compounds have the property of prolonging the life of a test animal when the adrenal gland of this animal has been removed.

A peculiar place is taken by the so-called progesterone, which compound has a 3-keto-Δ^4 system in the ring A and an acetyl group in the 17-position. This compound also is substituted by a methyl group on the carbon atoms 10 and 13. Progesterone is a hormone which controls the course of pregnancy in a high degree.

In after years, a large number of other steroid-like compounds having differing properties have been synthetized. Examples are: 16 - (x - aminoalkyl) - 4 - pregnene - 3 - 20 diones and acyl derivatives thereof, which compounds inhibit the activity of progesterone (U.S. Patent Specification 2,794,915). 14 - α - hydroxy - 11 - desoxycorticosterone and hydroxy compounds acylated in the 21-position. These compounds are stated to have anaesthetic, oestrogenic, testoid, folliculoid and luteoid activity (U.S. Patent Specification 2,727,911).

9 - x - fluoro- 4 - pregnene - 11β, 17x,21 - trihydroxy - 3,20 - diketo - 21 - tertiary butylacetate. As compared with hydrocortisone acetate this ester has a high systemic and strongly local activity (U.S. Patent Specification 2,736,681).

Δ1,4 - 3,20 - diketo - 11 - keto - or 11 - hydroxy - 17α, 21, - dihydroxypregna - diene - 21 - tertiary butylacetate and 9 - fluoro-derivatives thereof are stated to have cortisone activity but differ from cortisone by a reduced sodium or water retention (U.S. Patent Specification 2,736,734), 16α-hydroxy-$\Delta^{1,4}$-pregnadiene or the 9 (α) halogen derivatives thereof. These compounds are stated to be useful for combating inflammatory

phenomena, arthritis, asthma, and bursitis (U.S. Patent Specification 2,789,118). Δ4,8(9) - 3,20 diketo - 11,17 - dihydroxy - 21 - keto or 21 - hydroxypregnadienes are stated to have properties related to those of cortisone but fewer side effects and in particular a smaller sodium or water retention (U.S. Patent Specification 2,808,415).

In all the above-mentioned compounds, a methyl group is present in the 10- and 13-positions of the steroid skeleton, with the exception of the compounds related to oestrone, which have no 10-methyl group.

Steroid-like compounds having interesting pharmacological activity have also been prepared which, similarly to oestrone, lack a methyl group in the 10-position (so-called 19-nor-compounds). Of these compounds we mention: 9α-halogen-11β, 17β-dihydroxy-17α - methyl - 19 - norandrostane - 3 - ones. These compounds are stated to have strong anabolic and androgenic properties. (U.S. Patent Specification 2,806,863). It is stated that 19-nor-testosterones acylated in the 17-position have a similar activity (U.S. Patent Specification 2,798,879).

It is also known that the activity of 19-nor-androstanolone is several times higher than that of progesterone, and that esters of 19-nor-androstanolone and lower aliphatic carboxylic acids have smaller androgenic properties than, for example, testoterone, however, they have retained a considerable part of the anabolic activity of the androgenic hormones (U.S. Patent Specification 2,756,244). Although, as will be seen from the above, many steroid-like compounds are known which have either a methyl group in the 10-position or no methyl group in this position of the steroid skeleton, no attention was paid to the influence of the α- or β-configuration of the 10-methyl group upon the pharmacological properties of steroids. In this connection, it should be noted that in all the above-mentioned 10-methyl compounds the methyl group is in β-configuration. A considerable number of other steroid-like compounds are also known in which the 10-methyl group has an α-configuration, however, no pharmacological activity is described for any of these compounds. The above specifically relates to compounds described in Journal of the Chemical Society 1955, pages 2176 to 2190, Berichte 69, page 1123 (1936) and Journal of the Chemical Society 1938, page 869. All these known 10(α)-methyl steroids have a hydrocarbon radical containing 8 or 9 carbon atoms which are identical to those of cholesterol or ergosterol, respectively, in the 17-position of the steroid skeleton.

This invention relates to certain novel steroid compounds and methods of preparing the same. According to the present invention, there is provided a class of new compounds which compounds have the general formula A shown in the accompanying drawings, in which formula:—

R_1 represents hydrogen or a methyl group,

R_2 represents one or more double bonds at one or more of positions 1, 2, 3, 4, 5, 6, 15 and 16, or represents no double bonds (i.e. that the ring system is saturated),

R_3 represents hydrogen, a methyl or ethyl group, or a hydroxy or etherified or esterified hydroxy group,

R_4 represents a keto group or a hydroxy or etherified or esterified hydroxy group,

R_5 represents hydrogen or a halogen atom,

R_6 represents hydrogen, a methyl group, a halogen atom, or a hydroxy or etherified or esterified hydroxy group,

R_7 represents hydrogen or a halogen atom,

R_8 represents hydrogen or a hydroxy group or keto group,

R_9 represents hydrogen or a saturated or unsaturated hydrocarbon radical containing from 1 to 6 carbon atoms or such radical in which one or more hydrogen atoms are replaced by one or more hydroxy or etherified or esterified hydroxy groups and/or by double-bonded oxygen atoms,

R_{10} represents hydrogen or a hydroxy or etherified or esterified hydroxy group, R_9 and R_{10} being not both hydrogen,

or R_9 and R_{10} together represent a keto group, that is to say, an oxygen atom connected by a double bond to the 17-carbon atom in the nucleus,

and R_{11} represents hydrogen or a hydroxy or etherified or esterified hydroxy group.

In these compounds, the methyl group at the 10-position has the α-configuration, and is so represented in the drawings by the bond joining it to the steroid nucleus being in dash-line. This configuration is the same as in dihydroiso-lumisterone, a known compound related to lumisterol obtainable by ultraviolet irradiation of ergosterol and a convenient and preferred starting material from which to prepare compounds according to the present specification. In the majority of naturally-occurring steroid compounds, a 10-methyl group has the opposite, or β-configuration. The configuration of the hydrogen atom (or other substituent R_7) at the 9-position is the same as in dihydroiso-lumisterone. The absolute configuration at this position is not certain; it is now believed to be β, although formerly thought to be α. The configuration at the 9-position is therefore shown in the drawings as being β. Our Specification No. 12026/59 (Serial No. 929,272) relates to compounds having a configuration at the 9-position opposite to dihydroiso-lumisterone; these compounds, having the same 9-configuration as pyrocalciferol (i.e., 9- α-compounds) may be designated as of the pyro-series, as opposed to the lumi-series compris-

ing compounds according to the present invention.

The configuration at other positions in compounds derived eventually from lumisterol is not in all cases certain; in respect of positions 8, 13 and 14 it is believed to be 8β, 13β, 14α: compounds according to the present invention have the same configurations at these positions as dihydroiso-lumisterone. The configurations at other positions, unless explicitly specified otherwise, may be α or β. In these respects, the configurations are not significant, the most essential configurational features in compounds according to the parent application and the present invention being the 10 α-methyl group with a β-configuration of any hydrogen atom or substituent R_7 at the 9-position.

The accompanying drawings include a representation of a residue designated $X=$ which is identical with Formula A with R_9 and R_{10} being replaced by two bonds connecting two monovalent or one bivalent functional group or groups to the residue $X=$, i.e. at the 17-position of the steroid nucleus. Hereinafter, the formulæ of compounds will be described with reference to the residue $X=$, in which substituents R_1 to R_8 and R_{11} are as defined above unless otherwise defined in a more limited sense. It will be understood, moreover, that the definitions of the said substituents automatically preclude certain combinations; for example, a keto group at positions 3 will preclude an immediately-adjacent double bond (i.e. at 2- or 3- respectively), while always, double bonds in both of two immediately-adjacent positions are precluded. When a Δ^{16} double bond is present, then R_{16} or $R_{16'}$ in Formula A is eliminated, and residue X becomes monovalent at the 17-position.

Particularly useful compounds comprise those in which, in the residue $X=$, R_1, R_2, R_6, R_8, R_7, and R_{11} represent hydrogen, R_4 represents no double bonds or one or more double bonds at one or more of positions 1, 3, 4, 5 and/or 6, R_3 is a keto group or a hydroxy or etherified or esterified hydroxy group, and R_5 is hydrogen or a keto or hydroxy group. Another advantageous class of compounds is that in which, in the residue $X=$, and one or more of the substituents R_4, R_6 and R_7 consist of fluorine or chlorine atoms. Preferred arrangements of double bonds in the residue $X=$ comprise the completely saturated nuclear structure (i.e. R_4 represents no double bonds); one double bond at position 4; two double bonds at positions 1 and 4, or 4 and 6, or 3 and 5; three double bonds at positions 1, 4 and 6 or 1, 3 and 5. When a double bond is present at position 3, R_4 preferably represents an etherified or esterified hydroxy group. With the other preferred double bond arrangements mentioned, R_4 may most usefully be a keto group, or (especially when R_4 represents one double bond at position 4), a hydroxy group. Any hydroxy groups present may be etherified with a lower aliphatic alcohol (i.e. 1 to 6 carbon atoms) or mixed aliphatic-aromatic alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, or benzyl alcohol. Alternatively, said hydroxy groups may be esterified with a saturated or unsaturated, mono- or di-basic, aliphatic or aromatic carboxylic acid, for example, aliphatic carboxylic acids with 1 to 10 C-atoms, preferably 5 to 8 C-atoms and particularly. pentane carboxylic acid. Desired arrangements of double bonds or other substituents in the nucleus may be obtained in various manners described herein or otherwise known with reference to the preparation of other steroid compounds. The ensuing description is more particularly concerned with processes for procuring a desired C^{17}-side-chain.

The accompanying drawings further comprise a schematic diagram of a reaction scheme described in full herein, for degradation of the C-17 side chain, as well as certain individual structural formulæ. In certain cases when the radical $X=$ contains one hydrogen atom at the 17-position (i.e., R_9 or R_{16} represents hydrogen), then such hydrogen atom may be not shown, but the radical shown as monovalent.

Reference herein particularly in the claims to the residue X having resultantly the same substituents and double bond structure in a starting material for any particular reaction step, as in the product obtained thereby, denotes that substituents and structure in the starting material either are the same as in the product being unchanged during the reactional or are such that alterations produced therein during the reaction give the substituents and structure desired in the product as defined; for example, as is mentioned in relevant parts of the ensuing description, a reduction operation performed on the 17-side chain may involve elimination of double bonds and/or reduction of a keto group to a hydroxy group particularly at position 4; or an oxidation reaction may involve also oxidation of a. hydroxy to a keto group and may require protection for certain double bonds.

Our Specifications 636/63, 637/63, 638/63 and 639/63 (Serial Nos. 929,276, 929,277, 929,278 and 929,279) describe and claim respectively compounds of formulæ C and D; compounds of formulæ F and G; compounds of formulæ J and M; and compounds or formulate Z_{1a} and Z_5 including compounds of formulæ R and P, and in each case the preparation of said compounds, all of which are further described hereinafter with reference to the reaction scheme aforesaid.

It has been found that these compounds have no androgenic and no oestrogenic activity and that the absence of these two properties increases the selective activity of the compounds.

Furthermore, the invention relates to compounds which may serve as intermediate products for preparing the above-mentioned compounds.

An important subgroup of the compounds in accordance with the invention comprises compounds according to the above-mentioned formula, in which R_1, R_2, R_3, R_6, R_7 and R_{11} are hydrogen atoms, R_5 is a single bond or is a double-bond at at least one of the positions 1, 3, 4, 5, and 6, R_4 is a keto or hydroxy group or an etherified or esterified hydroxy group, R_8 is a hydrogen atom, a keto- or hydroxy group, R_9 is a methyl, ethinyl, ethylidene, ethyl, acetyl, hydroxylated acetyl group or a hydroxylated acetyl group the hydroxyl group of which is esterified or etherified, and R_{10} is a hydroxy group which may be esterified or etherified or a hydrogen atom, or R_8 and R_{10} together form a keto group.

The compounds of the following list contain the expression "lumi-". This indicates that the configuration of the 10-methyl group is identical to that of lumisterol. Furthermore, it can be assumed that the structure of the skeleton of these "lumi-steroids" is equal to that of lumistanol. However, there is no certainty on this point.

$\Delta^{1,4}$ - lumi - pregnadien - 17α - ol - 3,20 - dione
Δ^{1} - lumi - allopregnen - 11α - ol - 3,20 - dione
$\Delta^{1,4}$ - lumi - pregnadiene - 11β, 17α, 21 - triol - 3,20 - dione
$\Delta^{1,4}$ - 6α (or β) - lumi - methyl - pregna - diene-11β, 17α, 21-triole-3,20-dion
Δ^{1} - 17α - methyl - lumi - androsten - 17β-ol-3-one
$\Delta^{1,4}$ - 9β - fluoro - 11β, 16α, 17α, 21 - tetra - hydroxy - lumi - pregnadiene - 3,20 - dione
$\Delta^{1,4}$ - 9β - fluoro - 11β, 17α, 21 - tri - hydroxy-lumi-pregnadiene-3,20-dione
$\Delta^{1,4}$ - 6α - methyl - 11β, 17α, 21 - tri - hydroxy-lumi-pregnadiene-3,20-dione
2α-methyl-lumi-testosterone
2α - methyl - Δ^{4} - 9β - fluoro - 11β, 17α, 21 - trihydroxy - lumi - pregnene - 3,20 - dione
2α-methyldihydro-lumi-testosterone
2α - methyl - Δ^{4} - 11β, 17α, 21 - tri - hydroxy-lumi-pregnene-3,20-dione
2β-hydroxy-lumi-testosterone
3α - hydroxy - 11,20 - dioxo - lumi - pregnane-3-hemisuccinate
4-methyl-lumi-testosterone
Δ^{4} - lumi - pregnen - 3β - ol - 20 - one
4-chloro-lumi-testosterone
4-hydroxy-lumi-progesterone
4-chloro-lumi-progesterone
6β - hydroxy - 17α - methyl - lumi - testosterone
6β, 17β - dihydroxy - lumi - androstan - 3-one
6α, and β-fluor-lumiprogesterone
6α, and β - fluor - 17α - acetoxy - lumi - progesterone
6α, and β-methyl-lumiprogesterone
6α, and β-methyl-lumitestosterone
6α, and β - methyl - 17α - ethinyl - lumi - testosterone
6α, and β - 21 - dimethyl - 17α - ethinyl - lumitestosterone
6α, and β, 17α - dimethyl - lumitesto - sterone
6α, and β, 17α - dimethyl - 19 - nor - lumitestosterone
6α, and β - methyl - 11α - hydroxy - lumi - progesterone
6α, and β - methyl - hydro - lumi - cortisone
Δ^{6}-dehydro-lumiprogesterone
9β - fluor - 11β, 17α, 21 - trihydroxy - Δ^{4}-lumi-pregnene-3,29-dione
9β - fluoro - 11β, 16α 17α, 21 - tetra - hydroxy - Δ^{4} - lumi - pregnene - 3,20 - dione
9β - fluoro - 17β - hydroxy - 17α - methyl - Δ^{4} - lumi - androstene - 3,11 - dione
11β-hydroxy-lumiprogesterone
11β-hydroxy-lumitestosterone
11β, 17α, 21 - trihydroxy - Δ^{4} - lumi - pregnene-3,20-dione
17α, 21 - dihydroxy - Δ^{4} - lumi - preg - nene-3,11,20-trione
Δ^{5} - lumi - androstene - 3β, 16α (and β) - diol
16α-hydroxy-lumitestosterone
17α - methyl - Δ^{4} - lumi - androstene - 3β, 17β-diol
17α-methyl-lumitestosterone
17α-ethinyl-lumitestosterone
17α-vinyl-lumitestosterone
17α-ethyl-lumitestosterone
17α-hydroxy-lumiprogesterone
17α 21-dihydroxy-lumiprogesterone
17α - methyl - 21 - hydroxy - lumi - progesterone
Δ^{4}-lumi-androstene-3,17-dione
21-hydroxy-lumiprogesterone

The absolute configuration of the hydrogen atoms on the carbon atom 9 of these compounds was formerly assumed that in the compounds derived from lumisterol the hydrogen atom on the carbon atom 9 occupies the α-position (Fieser and Fieser, Natural products related to Phenanthrene, third edition, 1949, page 173 sqq). More recent investigations (Castells, Proc. of the Chem. Soc. 1958, 7), have, however, led to an opposite conclusion which is adopted in this specification.

As has been mentioned hereinbefore, the

compounds in accordance with the invention have no androgenic and no oestrogenic activity. These two properties combined with the specific activity of each substance affect highly positively the selective activity of the substances. For this reason, the invention is of particular importance for applications in which the androgenic and/or oestrogenic activities are considered as undesirable side effects.

A group of the compounds in accordance with the invention comprises substances which are progestationally active. It is very remarkable that these compounds produce their effects not only on injection but also with oral application. As a further peculiarity it can be mentioned that this group of substances does not show anti-oestrogenic activity.

This group of substances comprises compounds having the general formula A where R_1, R_3, R_5, R_6, R_7, R_8 and R_{11} are all hydrogen, R_4 is a keto group, a hydroxy- or an etherified or esterified hydroxy group, R_2 is a double-bond at the 4-position or two double-bonds at the 4- and 6-positions or two double-bonds at the 3- and 5-positions, in which latter event R_4 represents an etherified or esterified hydroxy group, R_9 is a hydrogen atom, a saturated or unsaturated alkyl group containing from 1 to 3 carbon atoms which may contain a double-bond oxygen atom and/or a hydroxy- or an etherified or esterified hydroxy group, and R_{10} is a hydrogen atom (however, R_9 and R_{10} cannot both be hydrogen atoms) or a hydroxy group or an etherified or esterified hydroxy group, or R_9 and R_{10} together form a keto group.

In particular, this group of substances includes a class for which R_1, R_2 and R_{10} have the meaning given in the preceding paragraph and R_9 is a hydrogen atom or a $-CO\,.\,CH_3$, $-CH_2-CH_3$, $-CH=CH_2$, $-C\equiv CH$, $-CO-CH_2OH$ group, in which latter group the hydroxy group may be etherified or esterified, however, R_9 and R_{10} together can be a keto group but cannot both be hydrogen atoms. Examples of these compounds are indicated by the formulæ VIII, XI, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXVII, XXXIII, XXXIV, XXXV, XXXVI, XXXVII, XXXVIII. It should be noted that the progestational activity of the above-mentioned compound, when these contain a $-CO-CH_3$ group and a hydroxy group, both on the carbon atom 17, is lower compared with the corresponding compounds of which the 17-hydroxy group is esterified.

Of the ether groups, we may mention the ethers of lower aliphatic alcohols, or of aliphatic aromatic alcohols, for example, methanol, ethanol, propylalcohol, butanol or benzyl alcohol.

Examples of the ester groups are given in the Examples 7, 10, 20 and 23.

It has also been found that compounds having the general formula A wherein R_1, R_3, R_5, R_6, R_7, R_8 and R_{11} are all hydrogen, R_4 is a keto group, a hydroxy or an etherified or esterified hydroxy group, R_2 is a double-bond at the 4-position or two double-bonds at the 4- and 6-positions or two double-bonds at the 3- and 5-positions, in which latter event R_4 is an esterified or etherified hydroxy group, and R_9 is a keto group or a hydroxy group of an etherified or an esterified hydroxy group and R_{10} is hydrogen, produce an anabolic effect in addition to a non-androgenic, non-oestrogenic, non-anti-oestrogenic and a progestational activity.

Of the ether group, we may mention the ethers of lower aliphatic alcohols or of aliphatic-aromatic alcohols, for example methanol, ethanol, propyl alcohol, butanol or benzyl alcohol.

Of the ester groups examples are mentioned in Examples 7, 10, 20 and 23.

The various biological effects were determined in the following test experiments.

1. Androgenic and anti-androgenic activity. These effects are measured by determining the weight of the seminal vesicle, the weight of the ventral prostate both in infantile and in castrated male rats which may have been pretreated with an androgenic substance.

2. Oestrogenic and anti-oestrogenic activities. These effects are measured by determining the weight of the uterus of infantile and sprayed female rats by means of the vaginal smear of adult female rats and the vaginal aperture of infantile female rate, which may have been treated with an oestrogenic substance.

3. Progestational activity. This effect is determined after subcutaneous intramuscular or oral administration to infantile female rabbits having a weight of from 600 to 800 gms with respect to the uterus and according to the technique of Clauberg.

4. Anabolic Activity. This effect is determined by the effect in the renotropic test (weight increase of the kidney) in castrated adult male mice. This is done since we think that the musculus levator ani test depends upon the sex, that is to say, that the musculus levator ani will not increase its weight if there is no male activity, and this property is not present in the compounds in accordance with the invention.

5. Anti-ovulation activity. This effect has been measured on adult female rats which, after application of the substance and during this application, were brought into contact with male partners during two sexual cycles, after which the occurrence of fertilization is ascertained a fortnight after the removal of the male partners.

6. Anti-inflammatory activity. This effect was measured by arranging pledgets subcutaneously in adult male rats with the result

that their bodies react with inflammatory effect. By the action of several substances (hydrocortisone) this inflammatory effect is eliminated. The inflammatory effect mentioned in this application is intensification of the normally occurring inflammatory effect.

The properties of a number of compounds in accordance with the invention are summed up hereinafter.

The lumiprogesterone (Formula VIII) has no androgenic or oestrogenic activities. It is orally progestational and not anti-oestrogenic. In this connection, it should be noted that progesterone is androgenic and not orally active and that the progestational effect is five times weaker than that of lumiprogesterone. In addition, lumiprogesterone has a strongly inhibiting effect upon the ovulation, and progesterone lacks this property.

The Δ6-dehydro-lumiprogesterone. (Formula XXVII) is parentally, progestationally active in a degree which is 5 to 4 times stronger than that of lumiprogesterone. The orally progestational activity of Δ6-dehydro-lumiprogesterone is at least 20 times stronger than that of a lumi-progesterone. The Δ6-dehydro-progesterone has no androgenic and no oestrogenic activity, nor is it anti-oestrogenically active. In addition, the compound is not anabolically active and has a stronger anti-ovulation activity than lumiprogesterone.

The Δ6-dehydro-lumitestosterone. (Formula XX) has no androgenic and no oestrogenic activity. It is orally progestationally active and non anti-oestrogenic. The anti-androgenic activity of this compound and its capacity to produce an anabolic effect are highly interesting.

The 17α-ethinyl-lumitestosterone (Formula XXII) has no androgenic and no oestrogenic activity. It is orally progestationally active and not anti-oestrogenically active. The progestational activity exceeds that of progesterone.

The lumi-androstenedione (Formula XVI) is not androgenically and not oestrogenically active. Neither is it anti-oestrogenically active. The compound shows an orally progestational activity and has no anabolic activity.

The lumitestosterone (Formula XVIII) does not resemble the corresponding testosterone from the 10β-series with respect to its properties. It has no androgenic activity and is not active oestrogenically. It is orally active progestationally and not anti-oestrogenically. Furthermore, it has an anabolic effect.

The 17-acetate of 17α-hydroxy-lumiprogesterone (Formula XXXV) is not active androgenically nor oestrogenically. The progestational activity of this compound is 25 to 30 times that of lumiprogesterone. It is orally active and has a prolonged effect compared with progesterone. The compound has no anti-oestrogenic activity.

The 17-caproate of 17α-hydroxy-lumiprogesterone (Formula XXXVI) has no androgenic and no oestrogenic activities. The compound is progestationally active and this activity is twice that of lumiprogesterone. The compound is orally active and has a highly prolonged activity which exceeds that of the 17-acetate. The compound has no anti-oestrogenic activity.

The 3,17-di-acetate of 17α-hydroxy-lumiprogesterone (Formula XXXIV) (3,17 di-acetoxy $\Delta^{3,5}$ lumipregnadiene) has no androgenic and no oestrogenic activities. Its progestational activity is many times greater than that of lumiprogesterone. This activity is about equal to that of the 17-monoacetate of the 17α-hydroxy-lumiprogesterone. It is also orally active and has a prolonged activity exceeding that of the mono-acetate. Furthermore, it is not active anti-oestrogenically.

The 17-acetate of Δ6-dehydro-17α-hydroxy-lumi-progesterone (Formula XXXVIII) has no androgenic and no oestrogenic activities. Its progestational activity is many times that of Δ6-dehydro-lumiprogesterone. It is orally active and its activity is prolonged as compared with that of progesterone. Furthermore, it has no anti-oestrogenic activity.

The lumi-androst-4-ene-3,17β-diol (Formula XVII) has no androgenic and no oestrogenic activities. It is orally progestationally active and has no anti-oestrogenic activity. Furthermore, it has an anabolic effect.

The lumi-testosterone-17β-(β-phenylpropionate) (Formula XIX) has no androgenic and no oestrogenic activity. Furthermore, it is orally progestationally active and has no anti-oestrogenic properties. It is anabolically active and shows an anti-androgenic effect.

The Δ6-dehydro-lumitestosterone-17β-propionate (Formula XXI) has no androgenic and no oestrogenic activity. It is orally progestationally active and has no anti-oestrogenic activity. Furthermore, it has an anabolic activity and produces an anti-androgenic effect.

The lumi-desoxycorticosterone-21-acetate (Formula XI) has no androgenic and no oestrogenic activities. It is orally progestationally active and shows no anti-oestrogenic effect. In addition, it produces an inflammatory effect in the anti-inflammatory test.

Methods of Preparing the Compounds According to the Invention

The active compounds of the medicines according to the invention and furthermore the compounds in accordance with the invention and their intermediate products can be prepared according to methods which, in general, are known for preparing the corresponding 10β-methyl steroids. One of the difficulties met with in this synthesis is the introduction of the 10α-methyl group, since hitherto there is no suitable method of con-

verting a 10β-methyl group into a 10α-methyl group for any compound of the steroid series. Hence, in order to prepare the compounds in accordance with the invention, preferably use is made of starting products in which the 10α-methyl configuration is already present.

Known steroids having a 10α-methyl grouping are, for example, lumisterol$_2$ and lumisterol$_3$. (These compounds are produced by ultraviolet irradiation of ergisterol and 7-dehydrocholesterol, respectively).

The said lumi-steroids are very suitable starting materials for the preparation of the compounds in accordance with the invention.

Obviously, there are other possibilities of preparing lumisteroids which are suitable for preparing compounds in accordance with the invention. The lumi-structure may be introduced in the presence of other side chains than the chains mentioned with respect to the carbon atom 17, by irradiation of Δ5,7 similar compounds.

One may start from compounds in which the side chain is a hydroxy group or from compounds in which the side chain represents that of sapogenins, for example diosgenin.

The compounds in accordance with the invention may be prepared by methods which are known *per se* for the preparation of analogous compounds, provided that as the starting product a compound is chosen which contains the 10α-methyl group.

One method of preparing the compounds in accordance with the invention is shown diagrammatically in the accompanying drawings. As the starting product, use is made of a compound having the general formula B.

In this formula B, X is a lumi-steroid group having the structure which is also given in drawings. In the group X, R_1 to R_8 and R_{11} have the above-mentioned meanings. Q^I and Q^{II} are lower aliphatic hydrocarbon radicals containing from 1 to 6 carbon atoms, while one of these groups may also be a hydrogen atom. A group of highly suitable starting materials is that in which Q^I is a 3-methyl-butanyl-2 group and Q^{II} is a hydrogen atom. By oxidative decomposition, followed if desired by conversion into an acid chloride or ester, these starting compounds are converted into compounds having the general formula C. Q^{III} represents an H-atom or halogen atom or an OH-group or alkoxy group. The compounds according to the formula C are subsequently converted into compounds of the formula D. This group of substances includes the enamines and the enol-acylates, when Q^V represents a hydrogen atom and Q^{IV} a radical of a secondary amine or an O-acyl radical, and also substances in which Q^{IV} represents a hydrogen atom and Q^V a lower aliphatic hydrocarbon radical or a phenyl radical, or in which Q^{IV} and Q^V both are a lower aliphatic hydrocarbon radical or a phenyl radical. The term "lower aliphatic" herein denotes containing one to six carbon atoms, unless otherwise specified.

By oxidation of compounds having the formula D compounds having the formula E are obtained.

The compounds having the formulas C, D and E are suitable starting products for the preparation of other important intermediate products in preparing compounds in accordance with the invention. From the said groups of compounds, compounds having the formula J can be produced. In these compounds, Q^{VI} is a hydrogen atom or a methyl group and Q^{VII} an aldehyde group (or an addition compound thereof) or an O-acyl or a COO—R group, in which R is a lower aliphatic hydrocarbon radical containing from 1 to 6 carbon atoms. By oxidation of compounds having the formula J, compounds are obtained having the formula K, and from these latter compounds there may be produced, by reduction of the 17-keto group or by addition of a metal-organic compound, if required succeeded by reduction, compounds in accordance with the invention, having the formula L, in which in the 17-position of the steroid skeleton there are provided groups R_9 and R_{10}, where R_9 is a hydroxy or an esterified hydroxy group and R_{10} is a hydrogen atom or R_9 is a saturated or unsaturated lower aliphatic hydrocarbon radical containing from 1 to 6 carbon atoms and R_{10} is a hydroxy or esterified hydroxy group.

Compounds having the formula N can be obtained by peroxidation of compounds having the formula J and subsequent hydrolysis of the produced epoxyformiates having the formula M.

Compounds having the formula E can be used as starting products for the preparation of compounds having the formula Q by condensation of the starting products with a diester of oxalic acid and subsequent conversion into an iodine compound having the formula P and acylation of this latter compound with the use of an alkali metal salt of an organic carboxylic acid.

Details of the above-mentioned preparation are given hereinafter.

Another method of preparing the compounds in accordance with the invention may comprise the oxidative decomposition of the saturated side chain of 10α-methyl steroids, for example of lumisterol$_3$ and lumistanol$_3$ for example with chromic acid, with the production of the corresponding 17-keto, 17-acetyl-compounds and the corresponding etio-, nor- and bisnor-cholene and cholene acids, which compounds form part of the compounds in accordance with the invention or can be converted into them.

The invention includes methods of preparing compounds of formula A, as will be described hereinafter.

CHAPTER I.

A compound of formula B can be subjected to oxidizing decomposition to obtain important intermediate products of the formula C. In these formulæ Q^I and Q^{II} represent lower aliphatic hydrocarbon radicals or one represents such radical and the other a hydrogen atom, and Q^{III} represents hydrogen or a hydroxyl group. This method is particularly important for the conversion of compounds of the formula B, wherein Q^I is a 3-methyl-butanyl-2-group and Q^{II} is a hydrogen atom and R_1, R_2, R_5, R_6, R_7, R_8 and R_{11} are hydrogen atoms and R_4 is a keto group or a hydroxy- or an etherified or esterified hydroxy-group and R_c represents one double bond or one to three double bonds in the A- and B-rings of the steroid skeleton.

If R_4 is an etherified hydroxy-group, it consists, for example, of an ether group of a lower aliphatic alcohol, of which examples were given above. Examples of esterified hydroxy-groups are found in the Examples 7, 10, 20 and 23. In the A- and B-rings are contained, for example, double bonds at the position 1, 4, 5, 7 or 3, in which last-mentioned case R_4 is an esterified or an etherified hydroxy-group and furthermore at the positions 1 and 4, 4 and 6, 4 and 7 or 3 and 5, in which latter case R_4 is an esterified or an etherified hydroxy-group, R_c may furthermore designate three double bonds at the positions 1, 4 and 6, or 3, 5 and 7, in which latter case R_4 is again an etherified or esterified hydroxy-group. Finally R_c may be three double bonds at the positions 1, 3, and 5, in which case R_c cannot be a keto- or unetherized or unesterified hydroxy-group. Any Δ^7-double bond present is removed at some convenient point in the ensuing reaction scheme, for example by migration to the Δ^6-position by treatment with dry HCl gas.

Preferred systems of R_4 and R_c are: 3-keto; 3-keto-Δ^4-dehydro-, 3-keto-$\Delta^{4,6}$-dehydro-, 3-keto-$\Delta^{1,4}$-dehydro-, 3-keto-$\Delta^{4,7}$-dehydro- etherized or esterified 3-hydroxy-$\Delta^{5,6}$-dehydro-, 3-hydroxy-Δ^4-dehydro-.

In order to increase the yield of the oxidation reaction it is desirable to protect a double bond, if it is not in conjugation with the 3-keto-group or with a double bond. The reactivity of the Δ^7-double bond, however, renders a protection superfluous.

The double bond may be protected by conversion into a dibromide, which may be obtained by a reaction of the compound with molecular bromine, if necessary dissolved in a solvent. The two bromine atoms can be readily separated out after the oxidizing decomposition by reducing the compound with zinc dust in glacial acetic acid.

A double bond may furthermore be protected by conversion into epoxide, for example, by a reaction with hydrogen peroxide in alkaline medium. The epoxide may be decomposed with KI in a weak acidic medium, for example, acetic acid, the double bond being regained.

For the oxidizing decomposition of a compound of the formula B a choice may be made between a fairly large number of oxidizing agents. For example, use may be made of chromic trioxide, potassium, sodium- or ammonium bichromate, furthermore potassium permanganate, but preferably ozone.

The reaction may be carried out both in a homogeneous and in a heterogeneous or in an aqueous medium. The compound to be oxidized may be present both in a dissolved and in a suspended state.

Suitable solvents are, for example, oxidation-resistant, aliphatic or aromatic, liquid hydrocarbons or mixtures thereof, such as the higher aliphatic hydrocarbons, e.g. petroleum ether, ligroin, petrol, or aromatic hydrocarbons, for instance benzene, toluene, mesitylene. Very suitable have proved to be, moreover, a number of halogenated, lower aliphatic hydrocarbons, for instance diethylene chloride, ethylene, dichloride, chloroform, carbon tetrachloride, and also monochlorobenzene. If the compound to be oxidized is subjected to the reaction in a suspended state, use is preferably made of a polar solvent, for instance, water, as a medium.

The oxidation with chromium trioxide may take place in an alkaline, or a neutral or an acid medium. An alkaline reaction medium is obtained, for instance, by adding to the mixture of the reaction constituents an organic tertiary nitrogen base, for example, pyridine, collidine, piperidine or quinoline. If the reaction is carried out in an acid medium, use is preferably made of acetic acid or other liquid lower aliphatic carboxylic acid with 1 to 10 carbon atoms, for example, propionic acid, butyric acid, valeric acid, hexanoic acid, heptanoic acid, nonanoic acid or isobutyric acid. The reaction may, as an alternative, be carried in the presence of a strong inorganic acid, preferably sulphuric acid.

If the oxidizing decomposition is carried out with potassium- or sodium- or ammonium-bichromate, it is desirable that the reaction medium should be acidic, which may be achieved by adding a strong inorganic acid, preferably sulphuric acid.

Oxidation with potassium permanganate may also be carried out in alkaline, neutral or acidic medium; the reaction conditions may be the same as referred to above for the oxidation with chromium trioxide.

As a rule, during the oxidation with chromium trioxide, potassium- or sodium-bichromate or potassium permanganate, the corresponding acids of the compounds indicated by the formula C are obtained, wherein Q^{III} is a hydroxy group.

However, the oxidizing decomposition of a compound of the formula B is preferably carried out with ozone. This can be very satisfactorily carried out by dissolving the compound in one of the aforesaid solvents, and by introducing ozone into the liquid.

It is advisable to keep the temperature low during the reaction, for example between −100° C. and +30° C., preferably between −80° C. and +10° C.

The concentration of the compound to be oxidized is not subjected to narrow limits. It lies, for example, between 0.5% by weight and the saturation concentrations. The selectivity of the reaction may be increased by adding an organic nitrogen base to the reaction mixture; especially pyridine yields satisfactory results. During the ozonisation an ozonide is produced, which, on decomposition, yields an acid or an aldehyde of the formula C. This decomposition may be carried out with the aid of reducing or oxidizing agents. Suitable reducing agents are, for example, zinc dust in acetic acid or iron powder in sulphuric acid; furthermore, aliphatic aldehydes, for example, formaldehyde, paraformaldehyde, acetaldehyde, propionaldehyde, butanol or aromatic aldehydes such as benzaldehyde, and, moreover, saccharadoidal aldehydes such as glucose or a pentose. The decomposition of the ozonide is preferably carried out with mild reducing agents, if R_4 and R_5 are a 3-keto-$\Delta^{4,6}$- or 3-keto-$\Delta^{4,7}$-system. To this end the aforesaid aldehydes may be used. If the decomposition takes place by reduction, as a rule, aldehydes are obtained. With this reaction it is advantageous to process in an inert atmosphere, preferably in nitrogen, in order to prevent oxidation of the aldehyde obtained. As an oxidizing agent for the decomposition of the ozonide may be used, for example hydrogen peroxide or an alkaline solution of potassium permanganate to form an acid of Formula C.

This part of the invention is particularly important for the production of the aldehydes indicated by the formulae IV (Example 1b), XXVIII (Example 15b) and XXX (Example 15e).

Very suitable starting substances are, as is evident from the examples given in the preceding paragraph, $\Delta^{4,22}$-lumistadiene-3-one, $\Delta^{4,6,22}$-lumistatriene-3-one and $\Delta^{4,7,22}$-lumistatriene-3-one.

Chapter II.

Very important intermediate products for the production of compounds of formula A are compounds of the general formula D. In this formula Q^V is a hydrogen atom and Q^{IV} is either a secondary amine residue bound with the nitrogen atom to the same carbon atom to which also Q^V is bound, or an O-acyl group or a phenyl- or an alkyl-group, or both Q^{IV} and Q^V are each a phenyl or an alkyl group.

In general, the compounds of formula D may be produced from the compounds of formula C, wherein Q^{III} has the meaning referred to above, i.e. a hydrogen atom or a hydroxy group. For the production of compounds of formula D Q^{III} may also be an O-alkyl-group or a halogen atom. These compounds are obtained in known manner by esterifying an acid of the formula C or by halogenating it with a halogenation agent which is capable of replacing a hydroxy group in an acid by a halogen atom.

The production of the compounds of formula D from the compounds of the formula C may be carried out in various ways, in accordance with the meaning of Q^{III}, Q^{IV}, and Q^V. Various of these methods, known *per se*, from literature, are described briefly hereinafter.

The methods can be divided into two groups, for the first group indicated in this chapter by A Q^{III} is a hydrogen atom and Q^V likewise. In a second method, indicated by B, Q^{III} is an O-alkyl group or a hydroxy group and Q^V is a phenyl or an alkyl-group.

A). Q^{III} and Q^V are Hydrogen Atoms.

To this group are associated three methods, for the cases in which Q^{IV} is a secondary amine residue, an O-acyl-group, or a phenyl- or alkyl-group.

a). Q^{IV} is a Secondary Amine Residue.

The reaction is carried out by reacting an aldehyde of the formula C with a secondary amine in such conditions that water is separated out. As secondary amines may be used, for example, lower dialkyl amines with 1 to 6 carbon atoms in each alkyl group, or derivatives thereof, for example, diethylamine, di-isopropylamine, or dibutylamine; diaralkylamines such as dibenzylamine; or hydroxylated dialkylamines, such as diethanolamine, dimethanolamine, dipropanolamine, dibutanolamine, and dipentanolamine. Especially suitable are saturated cyclic amines, for example piperidine. It will be understood that, although the group Q^{IV} in enamine is designated a secondary amine residue, the enamine products are tertiary amines themselves.

It is essential that during reaction of the aldehyde with the secondary amine water should be separated out. In order to ensure this effect, a catalyst may be added to the reaction mixture whereby the separation of water is accelerated, for example, paratoluenesulphonic acid.

By subjecting the mixture during the reaction to azeotropic distillation, it is avoided that the water already formed should counteract the conversion into the desired final product. To this end use may be made of a suitable solvent in the reaction mixture, for example benzene or toluene. The water layer can be separated from the distillate, and the

layer of solvent may be fed back or not fed back to the reaction mixture. A very suitable method consists in that the distillate is dried by water-absorbing substances and by introducing again the dried solvent into the reaction mixture. Suitable water-absorbing substances compose inorganic oxides for example calcium oxide, barium oxide or alumina.

The reaction between aldehyde and secondary amine may be carried out in the presence of a solvent. To this end use may be made of, for example, aliphatic or aromatic solvents, for instance petroleum ether, ligroin, hexane, cyclohexane, benzene, toluene, xylene, or aliphatic ethers, for instance diethyl ether, diisopropyl-ether, dibutyl ether, di-isobutyl ether, or tetrahydrofuran. As an alternative, an excess quantity of a secondary base may be used as a solvent.

The temperature of the reaction is preferably chosen not to be too high, for example between 25 and 150° C. Very good results are obtained with a reaction temperature between 40 and 110° C. It should be noted that certain secondary amines could start side reactions, if a keto-group is present at the position 3 of the steroid skeleton, whether or not a Δ^4 double bond occurs in the molecule. In this case it is advisable to react equimolar quantities of the secondary base and the aldehyde and not to use an excess quantity of the base as a solvent.

This reaction is particularly suitable for the compounds of the general formula C, wherein X is a steroid group of the indicated meaning, on the understanding that R_1, R_2, R_3, R_4, R_7, R_8 and R_{11} are hydrogen atoms and R_4 and R_5 have the meanings referred to in Chapter I.

Particularly suitable starting products are steroids which contain a 3-keto-Δ^4, a 3-keto-$\Delta^{4,6}$, a 3-keto-$\Delta^{4,7}$-structure. This is explained more fully in the Examples 1e and 15c. With the choice of the said starting products enamines of, for example, the formula VI, XXIX respectively and furthermore a 3-keto-22-(N-enamino)-lumi-bis nor chola-4.6.20 (22)-triene are produced.

b) Q^{IV} IS AN O-ACYL-GROUP

For the production of these compounds an aldehyde of the formula C is reacted with a carboxylic acid anhydride in the presence of an alkali metal salt or the acid chloride of the same acid or of an organic tertiary N-base, for example, pyridine.

As an anhydride may be used that of a lower aliphatic carboxylic acid with 1 to 6 carbon atoms, for example, acetic acid, propionic acid, butyric acid, or valeric acid. As an alkali metal salt of the acid may be used, for example, the sodium- or potassium-salt.

Also this reaction must be carried out in the presence of a water binder or in such conditions that the formed water is separated out of the reaction medium during the reaction. In the aforesaid cases the acid anhydride or the acid chloride serves as a water binder. For this reason it is advisable to carry out the reaction of the aldehyde with an excess quantity of the acid anhydride of the acid chloride. Moreover, use may be made of inert solvents, for example, aliphatic or aromatic hydrocarbons, but these are not necessary. The temperature of the reaction is preferably between 10 and 150° C. and preferably between 30 and 110° C. It should be noted that, if the position 3 of the steroid skeleton is occupied by a keto-group, those complications inherent in the reaction indicated under A do not occur.

This reaction is described under Example 1f for the production of a compound of the formula VII.

c) Q^{IV} IS A PHENYL- OR ALKYL-GROUP.

This reaction is carried out by causing an aldehyde of the formula C to react with a phenyl- or alkyl-Grignard compound, for example phenyl magnesium bromide or the Grignard compound of a lower alkyl bromide with 1 to 6 carbon atoms, for example, methyl bromide, ethyl bromide, propyl bromide, isopropyl bromide, butyl bromide or isobutyl bromide. The reaction should take place in normal conditions for Grignard reactions, i.e. in anhydrous conditions, preferably in the presence of an aliphatic ether as a solvent. In this reaction an intermediate product is an O-Mg halide compound, which, by decomposition in a neutral or weak acidic medium, preferably in an aqueous medium, to which for example 2N hydrochloric acid or 2N sulphuric acid has been added, is converted into the corresponding hydroxy compound. This hydroxy compound is converted by withdrawing water, for example by heating *in vacuo*, with or without a water-absorbing agent being present, into a compound of the formula IV.

B. Q^{III} IS O-ALKYL OR HALOGEN, Q^{IV} AND Q^{V} ARE PHENYL- OR ALKYL-GROUPS.

a) Q^{III} IS O-ALKYL

This reaction is carried out by causing an ester of the formula C to react with a phenyl- or alkyl-Grignard compound. The ester consists in this case of an aliphatic ester, in which the alkyl-group is a lower aliphatic hydrocarbon radical with 1 to 6 carbon atoms, for example, a methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobutyl-, or pentyl-group. As a Grignard compound may be used, for example, phenyl magnesium bromide or methyl-, ethyl-, propyl-, isopropyl-, or butyl-magnesium bromide. The reaction may be carried out under the circumstances known for the Grignard reaction.

During the coupling reaction an OMg

halide-compound is formed intermediately, which, after decomposition with water or diluted aqueous acids, for example, diluted sulphuric acid or diluted hydrochloric acid, to form a hydroxy-compound, is subjected to water separation. This may be carried out by distilling the hydroxy compound to dryness, if necessary in the presence of a dehydrating agent, for example, by refluxing the compound with acetic acid anhydride and pyridine or by heating the substance with iodine in acetic acid anhydride or with acetic acid without more or with thionyl chloride, dissolved in toluene.

b) Q^{III} IS HALOGEN, FOR EXAMPLE, CHLORINE.

This reaction is carried out to cause an acid halide, for example the acid chloride or acid bromide of the formula C to react with diphenylcadmium or with a zinc Grignard compound, for example C_6H_5ZnCl. The ketone produced during this reaction is subjected to a Grignard reaction with phenyl- or alkyl-magnesium bromide, so that after the decomposition of the reaction product in an aqueous medium a hydroxy compound is produced in neutral or acidic medium, which compound yields by dehydration under the aforesaid circumstances (heating *in vacuo*, heating with acetic acid, heating with iodine in acetic acid anhydride) a compound of the formula D.

It should be noted that in accordance with the last-mentioned reaction, compounds can be obtained in which Q^{IV} and Q^{V} need not be identical and, for example Q^{VI} is a phenyl-group and Q^{V} is an aliphatic hydrocarbon radical with 1 to 6 carbon atoms.

It should furthermore be noted that in reactions A and B, any alkyl group represented by or contained in a group Q^{III}, Q^{IV} and/or Q^{V} is preferably an aliphatic hydrocarbon radical with 1 to 6 carbon atoms, particularly with 2 to 4 carbon atoms, for example, an ethyl- isopropyl-or propyl-group.

The reactions indicated under A and B of this chapter are of particular importance for the production of compounds of Formula D, wherein Q^{V} is a hydrogen atom and Q^{IV} an O-acyl group or a secondary amine residue. Particularly the O-acetyl compound and the piperidino-compound are very attractive final products of the present reaction.

The compounds of formula D are particularly important for the production of compounds of formula E (see Chapter III) or also of the formula J (see Chapter IV).

Finally it should be noted that isomers of the compounds of formula D are possible owing to asymmetry of the molecule around the $\Delta^{(20/22)}$ double bond.

For the preferred meaning of R_1 to R_8 and R_{11} in the reaction described in this Chapter (II) we refer to the first part of Chapter I.

CHAPTER III.

The compound of the general formula D obtained by the method described above are very suitable for the production of compound in which at the position 17 an acetyl group and a hydrogen atom are present. All these compounds are new and have not been previously described in literature. The compounds excel by particular physiological action, as hereinbefore described.

Compounds of the formula D may be oxidized into compounds of the formula E. The production takes place by oxidizing compounds of the formula D under mild conditions in order that no complete decomposition of the side chain at the carbon atom 17 takes place.

Oxidizing agents which may be used are: for example, ozone, chromium trioxide, sodium- or potassium- or ammonium-bichromate, potassium permanaganate. As a rule the oxidation takes place with ozone in a neutral medium, but the oxidation with the other means mentioned above may take place both in a acidic and in an alkaline medium. The temperature of the reaction is preferably fairly low, i.e. between −100 and +100° C.

For the oxidation with ozone use is generally made of a slightly lower reaction temperature that for the oxidation with the other agents referred to above. When using ozone the conventional reaction temperature lies between: −100 and +30° C., preferably between −80 and +10° C. For the other oxidation agents the reaction temperature may be slightly higher, for example between −20 and +100, preferably between −10 and +30° C. It is furthermore advisable, in order to avoid hydrolysis of the enamine, to add the compound to be oxidized slowly and in parts to the oxidation medium and also to carry out the oxidation with the use of non-oxidizable diluents. Suitable diluents are preferably oxidation-resistant aliphatic or aromatic hydrocarbons, for instance petroleum ether, ligroin, petrol, benzene, toluene, mesitylene. Very suitable are found to be halogenated lower aliphatic or aromatic hydrocarbons such as methylene dichloride, ethylene dichloride, chloroform, carbon tetrachloride or monochlorobenzene. The oxidation may take place both in a homogeneous and in a heterogeneous medium. The compound to be oxidized may be present both in a dissolved and in a suspended state. If the compounds to be oxidized are present in the suspended state in the reaction, use is preferably made of a polar solvent as a medium, for example water.

The oxidation with chromium trioxide may take place both in an alkaline, a neutral and an acidic medium. The alkality of the reaction medium is obtained for example, by add-

ing to the mixture of the reaction components an organic, tertiary nitrogen base, for example, pyridine, collidine, piperidine, chinoline, diethylaniline or dimethylaniline.

If the reaction is carried out in an acidic medium, this is preferably done in glacial acetic acid or other lower aliphatic, liquid carboxylic acid or mixtures thereof, for example, propionic acid, butyric acid, valeric acid, pentane carboxylic acid, hexane carboxylic acid, heptane carboxylic acid or isobutyric acid. However, the reaction may be carried out in the presence of an inorganic acid, preferably sulphuric acid. If the oxidizing decomposition takes place with potassium, sodium or ammonium bichromate, it is desirable that the reaction medium should be acidic. This is preferably attained by adding sulphuric acid or acetic acid. Oxidation with potassium permanganate may also make place in an alkaline, a neutral or an acidic medium. The reaction conditions may be the same as indicated above for the oxidation with chromium trioxide.

Since the oxidation with ozone takes place quantitatively, it is advisable to pass no greater quantity through the liquid containing the compound to be oxidized than is necessary for the desired oxidation. For the oxidation with the other aforesaid agents use may be made of a slight excess quantity of the oxidizing agent.

The concentration of the compound to be oxidized is not narrow limits. Satisfactory results are obtained, if the starting substance is available in a quantity of 0.1 to 20% by weight, preferably 1 to 10% by weight in the reaction medium. After oxidation with the solid, aforesaid oxidizing agents the substance obtained may be isolated in a conventional manner from the reaction mixture. When using an excess quantity of the oxidizing agent, it is advantageous to reduce it first with an adequate quantity of a lower aliphatic alcohol, for instance methanol or ethanol. Then the reaction mixture is poured out in water, after which it is extracted with an organic solvent, owing to which the ketone obtained is isolated in a practically pure state. If the oxidation takes place with ozone, it is necessary that the primarily produced oxidation product (ozonide) should be decomposed. This decomposition may take place with reducing or oxidizing agents.

As reducing agent use may be made of, for example, zinc dust in acetic acid or iron powder in sulphuric acid. Furthermore aliphatic or aromatic aldehydes, referred to in Chapter I, (for the decomposition of the ozonide) may be employed. They are preferably used, when mild reduction conditions are required, for example, in the presence of a 3-keto-$\Delta^{4,6}$-system.

As an oxidizing agent for the decomposition of the ozonide use may be made for example of hydrogen peroxide or an alkaline solution of potassium permanganate.

If in the ring A of the steroid skeleton prevails a double bond which is not in conjugation with the 3-keto group or with a carbon- carbon-double bond, it is advisable to protect this double bond from attack by the aforesaid oxidizing agents. This is, in general, not necessary in the case of a Δ^7-double bond. This protection and the subsequent regeneration of the initial system of the steroid skeleton may take place in the manner described in Chapter I.

Suitable starting substance for the production of compounds of Formula E are the compounds of the Formula D, which are described in the preceding part of the Specification. Particularly those compounds may be mentioned in which Q^V is a hydrogen atom and Q^{IV} is a secondary amino radical of which the N atom is bound to the carbon atom to which also Q^V is bound or an O-acyl radical. The secondary amino radical is preferably the piperidino-group, but also very suitable are found to be radicals of lower aliphatic secondary amines with 1 to 6 carbon atoms.

As such we may mention diethyl-, dipropyl di-isopropyl- or di-isobutylamine. Furthermore use may be made of hydroxylated derivatives of these amines, for example, diethanolamine, or dipropanolamine. As an example of an O-acyl-group reference is to be made, in particular, to those radicals in which the acyl-group is the radical of an aliphatic carboxylic acid with 1 to 6 carbon atoms. As such reference is to be made preferably as an O-acyl group to the O—$COCH_3$ (acetyl) group or moreover, to the propionyl-butyryl- and valeryl-group.

For the preferred meanings of R_1 to R_8 and R_{11} reference can be made to the first part of Chapter I.

Examples illustrating the method described in this chapter are 1g, 1h, and 15d. In this case lumiprogesterone (Formula VIII) and Δ^6-dehydro-lumiprogesterone (Formula XXVII) are formed.

Chapter IV.

Compounds having the formula J which are suitable for preparing compounds having the formula K, can be divided into three different groups J_1, J_2 and J_3.

Group J_1. This comprises the compounds for which Q^{VI} is a CH_3 group and Q^{VII} is an aldehyde group (or addition products thereof, i.e. with HCN or with bisulphite).

Group J_2 comprises substances for which Q^{VI} is a CH_3-group and Q^{VII} is a —O-acyl group.

Group J_3 comprises compounds for which Q^{VI} is hydrogen atom and Q^{VII} is a group —COOR and in which R is an aliphatic

hydrocarbon radical containing from 1 to 6 carbon atoms.

In this chapter the preparation of these groups J_1, J_2 and J_3 is described.

PREPARATION OF COMPOUNDS OF GROUP J_1.

Compounds of this group of substances can be produced in two manners.

According to the first method bromine is caused to act upon aldehydes of the formula C.

In this reaction, the α-hydrogen atom (with respect to the aldehyde group) is replaced by bromination with elemental bromine bromine with simultaneous formation of hydrogen bromide. By withdrawing HBr from the compounds produced (Formula G) compounds are obtained which belong to the group J_1. The bromination reaction can be performed satisfactorily by dissolving an aldehyde of the formula C in an aliphatic or aromatic hydrocarbon or a halogenated aliphatic or aromatic hydrocarbon, for example petroleum ether, ligroin, benzine, benzene, toluene, mesitylene, dichloroethane, chloroform, carbon, tetrachloride, or methylene chloride and adding to this solution a solution of bromine in one of the above-mentioned solvents. Preferably, the formation of the bromine substitution product is accelerated catalytically by exposure to light, for example, by irradiating the reaction mixture with a normal electric filament lamp. It is also very desirable for the reaction mixture to contain an HBr acceptor in order to bind the HBr produced in the substitution reaction. For this purpose use may be made of suspended calcium carbonate or calcium hydroxide. Use may also be made of pyridine or another nitrogen base. Since, however, these compounds can react with bromine with the formation of products which also have brominating properties, there is a possibility of by-product being formed.

Preferably the bromination is carried out at a temperature between 0° C. and 50° C., for example between 20° C. and 30° C. The duration of the reaction is from 1 to 3 hours. In order to avoid the formation of by-products as far as possible, it is also desirable for the bromine solution to be added at a slow rate and for the reaction mixture to contain an amount of bromine not exceeding that required for the formation of the bromine substitution product. It has also been found that the exclusion of oxygen from the reaction provides advantages and that for this reason the reaction is preferably performed in a nitrogen atmosphere.

The formation of by-products cannot be avoided without taking special precautions, if in the ring A of the steroid skeleton there is a 3-keto group and the allyl-position relative thereto, is occupied by a substitutable hydrogen atom since in this event substitution can also take place at the 2-position of the steroid skeleton.

If this grouping should be found in a suitable starting material, the reaction is preferably carried out according to the second method described hereinafter, which can also be used without difficulty if the starting material contains no 3-keto group.

According to the *second method* bromine is added to an enamine of the formula D, preferably the piperidino-enamine. In this formula, the piperidination may be replaced by another secondary amine.

The addition of bromine to these enamines is effected preferably at a comparatively low temperature, preferably at a temperature between −80° C. and 20° C., for example between −55° C. and 0° C.

It is also preferable for the reaction to be performed with equimolar amounts of bromine (that is to say, the amount required for the addition of 2 bromine atoms). The time required for this reaction is very short and as a rule, less than 15 minutes. Then, the dibromine-enamine (formula F) is dissolved, if required after isolation, in an organic solvent, for example an aliphatic or aromatic hydrocarbon or a halogenated aliphatic or aromatic hydrocarbon, after which water is added to this solution so that the dibromo-enamine is hydrolysed. The duration of this hydrolysis reaction is comparatively long, for example from 1 to 5 hours. Preferably, the reaction is performed while stirring vigorously and at a temperature between 0 and +50° C., preferably between +10° C. and +30° C. In this hydrolysis, an α-bromine compound of the above mentioned formula G is produced. After splitting off of HBr, a compound of the group J_1, and this is effected preferably in the presence of a basically reacting inorganic or organic compound, for example, as an inorganic compound a metal oxide or metal hydroxide, for example calcium oxide, calcium hydroxide, barium oxide, barium hydroxide or magnesium oxide may be used, or as an organic base a primary, secondary or tertiary nitrogen base, for example, as a primary amine, ethylamine, propylamine, butylamine, benzylamine, or aniline; or as a secondary amine, for example dimethylamine, diethylamine, dipropylamine, di-isopropylamine, dibutylamine, methylaniline, ethylaniline, or piperidine; or as a tertiary base, for example, trimethylamine, triethylamine, tripropylamine, tri-isopropylamine, tributylamine, trimethylaniline, diethylaniline, collidine, quinoline, isoquinoline, picoline, lutidine or pyridine. It should be noted that the splitting off of hydrobromic acid is preferably not carried out by means of a primary or secondary amine if the ring A of the steroid skeleton contains a 3-keto group. In this case, use is preferably made of a ter-

tiary hydrogen base or an inorganic base as the HBr-acceptor.

The aldehyde of the group J_1 in which Q^{VI} is a methyl group and Q^{VII} is a —CHO group obtained according to either of the two methods designated J_1 hereinbefore, is preferably subsequently converted into a HCN or bisulphite addition compound, before it is oxidized to form a compound having the formula K. The preparation of the HCN addition compound is preferred especially because this preparation proceeds comparatively simply. The HCN-addition-compound may be obtained by dissolving the corresponding aldehyde in a diluent for example, one of the above mentioned aliphatic or aromatic hydrocarbons, or by suspending it therein, and by adding a solution of sodium- or potassium-cyanide in a lower aliphatic alcohol, for example methanol, to this medium. Then acetic acid is cautiously added dropwise to this reaction mixture at a comparatively low temperature (for example −20° C.) for 1 hour. As a result, HCN is slowly produced, which adds to the carbonyl group to form the desired addition product. The reaction is completed by allowing the reaction mixture to stand for a considerable period of time (about 24 to 48 hours at −5°). *The bisulphite addition compound* can be produced by reacting the aldehyde with sodium bisulphite, for example in an aqueous methanolic solution. The formation of an addition compound is specifically desirable if R_2 represents at least one double bond in the steroid skeleton.

For the methods according to this part of the invention, particularly suitable compounds are those in which R_1, R_2, R_3, R_6, R_7, R_8 and R_{11} represent a hydrogen atom and R_2 and R_4 have the meaning of Chapter I, first paragraph, and first sentence of the second paragraph. This is explained more fully in the Examples 3a, 3b, 3c and 24 for the preparation of compounds having the formulas XIV, XV and XL which belong to the group J_1.

PREPARATION OF COMPOUNDS OF GROUP J_2.

In the compounds of this group Q^{VI} is a CH_3 and Q^{VII} a -O-acyl group. Acyl may be the acyl radical of an aliphatic carboxylic acid containing from 1 to 6 carbon atoms or of an aromatic carboxylic acid, for example of acetic acid, propionic acid, butyric acid, valeric acid, or of benzene carboxylic acid. However, preferably the acyl group is the acid radical of acetic acid. For preparing this group of substances, one can start from compounds having the general formula E. By acetylating compounds having this formula with isopropenylacylate preferably in the presence of catalytic amounts of concentrated sulphuric acid, enol acylates are produced. It is not necessary to add a diluent, for example a solvent, to the reaction mixture, since the isopropenyl acylate itself can be used as such. The reaction is preferably performed at the boiling point of the reaction mixture for from 1 to 15 hours. During the reaction, the acyl group is split off from the isopropenylacetate with the formation of the ketone which is slowly withdrawn from the reaction mixture by distillation. The enolacylate formed by this reaction has the structure according to Formula H. This compound can be converted into a compound of the group J_2, in which Q^{VI} is a methyl group and Q^{VII} an O-acyl, without intermediate isolation by adding to the reaction mixture a catalyst which is capable of shifting the double bond to the nucleus, for example, a small amount of paratoluene sulphonic acid preferably dissolved in acetic acid anhydride.

If, in a compound having the formula E, a readily enolisable grouping is present in the ring A of the steroid skeleton, for example 3-keto-Δ^1-; 3-keto-Δ^1-; 3-keto-$\Delta^{4,6}$- and 3-keto-$\Delta^{4,7}$-, in the above-mentioned reaction these configurations are entirely or partly re-arranged to form enol-acylate-groupings. The initial grouping can be recovered by iodinating the reaction product iodosuccinimide dissolved in dioxane and subsequent deiodination with sodium bisulphite. In this reaction, there is no or hardly any destruction of the grouping on the C_{17}-side chain.

For the methods according to this part of the invention particularly suitable compounds are those in which R_1, R_2, R_3, R_6, R_7, R_8 and R_{11} are a hydrogen atom and R_2 and R_4 have the meaning of Chapter I, first paragraph and first sentence of the second paragraph.

PREPARATION OF COMPOUNDS OF THE GROUP J_3.

Compounds belong to this group can be obtained by condensing a compound having the formula E with oxalic acid dialkyl esters, for example the diethyl ester, in the presence of an alkali metal alkoxide or equivalent condensation agent, for example sodium methylate. In this reaction, which preferably is performed in the presence of a solvent, for example a lower aliphatic alcohol, in particular a tertiary butyl alcohol, a compound is produced which can be considered as having the formula R in which M represents a metal atom and R the same alkyl radical as in the oxalate ester. If a solution of sodium acetate in glacial acetic acid and methanol is added to the reaction mixture and subsequently a solution of bromine, for example in chloroform, is also added thereto, a dibromo-reaction product is produced which, after decomposition with an alkaline medium such as an alkali metal alkanolate, for example sodium methylate or sodium ethylate, gives a compound of the group J_3, in which Q^{VI} is a

hydrogen atom and Q^{VII} is a COOR-group. This reaction which in spite of the comparatively complicated procedure can give a high yield, is preferably carried out with an excess of the oxalic acid dialkyl ester. If in the ring A of the steroid skeleton of the starting compound having the formula E a 3-keto group is present, the excess of the dialkyl oxalic acid ester attacks one of the carbon atoms of the ring A, for example in the 2- or 4-positions (however, the formation of such by-products does not occur if in these positions substituents are already present). If these impediments do not occur in the 3-keto compound of the formula E, the reaction with the excess of oxalic acid dialkyl ester after completion (bromination and subsequent decomposition with sodium methanolate) results in a 3-keto 2 or 4 bromine substitution product. This bromine atom may be split off by reduction with for example powdered zinc in glacial acetic acid, however, if desired, this bromine atom can be maintained or replaced by another group, for example a methyl group, or split off to produce a double bond between the carbon atoms 1 and 2 or 4 and 5.

Particularly suitable compounds for practising the method described above are those in which R_1, R_3, R_5, R_6, R_7, R_8 and R_{11} are hydrogen atoms and R_2 and R_4 have the meaning of Chapter I, first paragraph, and first sentence of the second paragraph.

Chapter V.

Compounds of the formula J may be oxidized to form compounds of the general formula K. In these formulae Q^{VI} is a methyl group and Q^{VII} is an aldehyde group or addition compounds thereof or an -O-acyl group or Q^{VI} is hydrogen and Q^{VII} a —COOR group, in which latter group R designates an aliphatic hydrocarbon radical with 1 to 6 carbon atoms. If Q^{VII} has the latter meaning, Q^{VI} is always a hydrogen atom. The oxidation can advantageously be carried out in the manner described for the oxidation of compounds of the general formula D to form compounds of the general formula E, i.e. suitable oxidizing agents are ozone, chromium trioxide, alkali metal salts of chromic acid, for example, sodium- or potassium-bichromate and furthermore potassium permanganate. The reaction may furthermore take place both in a homogeneous, a heterogeneous and aqueous medium. The compound to be oxidized may be available both in a dissolved and in a suspended state. If a compound to be oxidized is converted in a homogeneous medium, suitable solvents are in the first place aliphatic or aromatic hydrocarbons, for example petroleum ether, ligroin, petrol or aromatic hydrocarbons such as benzene, toluene or mesitylene. Very suitable are found to be, moreover, a few halogenated, lower aliphatic hydrocarbons, for example, methylene dichloride, ethylene dichloride, chloroform, carbon tetrachloride or monochlorobenzene. If the compound to be oxidized is available in a suspended state for the reaction, use is preferably made of a polar solvent as a medium, for instance water. The oxidation with ozone can be readily carried out and is therefore to be preferred over the use of the other aforesaid oxidizing agents. A compound of the formula J is preferably dissolved in one of the aforesaid aliphatic, aromatic or halogenated aromatic or aliphatic hydrocarbons, after which ozone-containing air or oxygen is passed through the solution. It is advisable to keep the reaction temperature low. Within the temperature region of −100 to +30° C., satisfactory results were obtained. In a temperature region from −80 to +10° C., the results were best. The concentration of the compound to be ozonized is not subjected to narrow limits; it amounts to for example 0.5% by weight and the saturation concentration. The selectivity of the ozonisation may be increased in the manner described in Chapter I.

During the ozonisation an ozonide is formed, which yields, after decomposition with reducing or oxidizing agents, a ketone of the formula K. As a reducing agent the agents referred to in Chapter I may be used. The decomposition of the ozonide is preferably carried out with mild reducing agents, if R_1 and R_2 designate a 3-keto-$\Delta^{4,6}$- or a 3-keto-$\Delta^{4,7}$-system. If the ozonide would be decomposed by oxidation into a compound of the formula K, use could be made, for example, of hydrogen peroxide or an alkaline solution of potassium permanganate. The oxidation of a compound of the formula J with chromium trioxide may take place both in an alkaline, a neutral or an acidic medium. An alkaline reaction medium is obtained, for example, by adding to the mixture of the reaction constituents an organic, tertiary nitrogen base, for instance, pyridine, collidine, piperidine, chinoline, dimethyl- or diethylaniline. If the reaction is carried out in an acidic medium this takes preferably place in the presence of a lower aliphatic carboxylic acid, for instance acetic acid, propionic acid, butyric acid, valeric acid, pentane carboxylic acid, hexane carboxylic acid, heptane carboxylic acid or isobutyric acid. Instead of using an aliphatic carboxylic acid, use may be made of an inorganic acid, preferably sulphuric acid. If the oxidation decomposition of a compound of the formula J takes place with potassium-, sodium, or ammonium bichromate, it is desirable that the reaction medium should be acidic. This is preferably achieved by adding sulphuric acid to the reaction medium.

Oxidation with potassium permanganate

may take place both in alkaline, neutral and acidic medium.

The reaction conditions may otherwise be the same as indicated above for the oxidation with chromium trioxide. The reaction is particularly suitable for being carrying out with those compounds in which Q^{VI} is a methyl group and Q^{VII} an aldehyde group or addition products of the latter compound (for instance HCN or bisulphite addition compounds). The starting compounds are, in particular, those in which R_1 to R_8 and R_{11} have the meanings described in the first part of Chapter I. Q^V is furthermore preferably a methyl group and Q^{VII} is a cyanhydrin group.

The advantage of the conversion of the aldehyde into an addition compound consists in that the aldehyde function in conjugation with a carbon-carbon double bond is fairly stable in oxidation, which is no longer the case when this structure is dissociated by the formation of addition compounds. It should finally be noted that the compounds obtained in accordance with this part of the invention have important pharmacologic properties and may be employed for the synthesis of new compounds, particularly, of compounds of the formula L. The compounds of the formula J may occur, owing to cis-transisomerisation about the double bond $\Delta^{17(20)}$ in two isomer configurations.

The method described in this chapter is set out more fully in the Examples 3b and 3c and 24 for the production of the compounds of the formulae XVI and XLII.

Chapter VI.

The invention relates furthermore to the production of compounds of the general formula L from compounds of the general formula K.

The compounds of the formula L contain two important subgroups, i.e.

1) one in which R_8 is a hydrogen atom and R_{10} is a hydroxy- or an etherified or esterified hydroxy-group,

2) a second group in which R_8 is a saturated or an unsaturated aliphatic hydrocarbon radical with 1 to 6 carbon atoms and in which R_{10} has the meaning indicated in the preceding paragraph.

The compounds of the first subgroup are produced by reducing compounds of the general formula K with a reducing agent which is suitable for converting ketones into secondary alcohols, for example, with a complex metal hydride, that is, containing two different metal atoms, for instance lithium-aluminium hydride, sodium-boron-hydride; or with aluminium-alkyl compounds for instance diethylaluminiumhydride, diisobutyl-aluminium hydride or triethylaluminium. The reduction may also be carried out by catalytic hydrogenation with, for instance, hydrogen gas and palladium, platinum or Raney nickel as a catalyst. The reduction may furthermore be carried out by Meerwein Pondorf's method with aluminium isopropylate. A further suitable reduction method is that using an alkali metal and a lower aliphatic mono- or dialcohol, for instance, sodium and ethanol, isopropanol, isobutanol or glycol. Finally a suitable reducing agent is moreover an alkali metal, and liquid ammonia, for example lithium and ammonia. These reductions are known from literature in details and need not be explained more fully.

If, previous to the reduction, the starting substance of the formula K contained ring A a 3-keto group, it can sometimes not be avoided that during the reduction of the 17-keto group also the 3-keto group is reduced. For the production of final products with a 3-keto group it is in these cases desirable that after the reduction a selective oxidation should take place to convert a 3-hydroxy into a 3-keto group. This oxidation may be carried out in the presence of a double bond in the allyl position relative to the 3-hydroxy group with manganese dioxide in an anhydrous medium at room temperature. Suitable solvents for the compound to be oxidized may be an aliphatic or aromatic hydrocarbon or a halogenated, aliphatic or aromatic hydrocarbon.

If it is desired to esterify either the 17-hydroxy or the 3-hydroxy group or both, this may take place by reacting the steroid concerned with an acid halide, for example the acidic chloride of an aliphatic carboxylic acid with 1 to 8 carbon atoms or an aromatic carboxylic acid preferably in the presence of pyridine to bind the hydrochloric acid set free. A suitable acid chloride is, for instance, acetic acid chloride or benzoyl chloride but more attractive is the use of an aliphatic acid chloride with 5 to 8, preferably 6 carbon atoms, since the 17-esters thus obtained, in accordance with other compounds, have a more favourable pharmacoligic activity and particularly a more prolonged activity than the esters having a lower number of carbon atoms.

If necessary, the reaction may be carried out with an acid anhydride instead of an acid chloride. Suitable acid anhydrides are, in particular, the anhydrides of the dibasic carboxylic acids, for instance, succinic anhydride. However, also the anhydrides of the said aliphatic carboxylic acids with 1 to 8 carbon atoms may be employed. Examples of this esterification are described in the Examples 6, 7, 9 and 10.

The compounds of the second subgroup are produced by reacting compounds of the general formula K with a Grignard reagent, metal acetylide, or other equivalent organometallic compound capable of reacting with a 17-keto group. This reaction is particularly

important for the production of those compounds in which R_9 is a saturated or an unsaturated aliphatic radical with 1 to 6 carbon atoms, preferably 1, 2 or 3 carbon atoms.

For this reaction in principle, two methods may be used. According to the first method a compound of the formula K is reacted with an aliphatic Grignard compound with 1 to 6 carbon atoms, in which the Mg—Hlg group is bound to a carbon atom which has no double bond. In the second method a compound of the formula K is caused to react with a triple unsaturated metal aliphatic compound, in which the metal atom is bound to one of the two triple unsaturated carbon atoms. Such compounds, derived from acetylene or substituted acetylenes, are designated acetylides. It should also be noted that this second method may also be used for producing compounds which are otherwise formed only in the first method, i.e. by hydrogenation of the unsaturated compounds obtained.

When using the Grignard reaction the normal conventional technique may be employed, i.e. an ethereal solution of a compound of the formula K reacts with methyl magnesium bromide, ethyl magnesium bromide, propyl magnesium bromide, butyl magnesium bromide or isobutyl magnesium bromide. If desired, use may be made of corresponding chlorine or iodine compounds.

The Grignard method is very suitable for the production of lumisteroids according to the invention having a β-hydroxy group and an α alkyl group at the position 17, for instance a methyl-, a $-C\equiv CH$, a $CH=CH_2$, a $-CH_2-CH_3$, a $-CH_2-C\equiv CH$ or $-CH_2-CH=CH_2$ group.

When using the second method use is preferably made of a lithium-, sodium- or potassium compound, for instance the ethynilide or the corresponding propargyl compound. The reaction may be carried out by dissolving an alkalimetal in liquid ammonia, passing a triple unsaturated aliphatic hydrocarbon through the mixture and by adding to this solution, which may contain an aliphatic ether, for instance, diethylether, tetrahydrofuran or petroleum ether as a diluent, a solution of a compound of the formula K. After hydrolysis of the intermediate metal compound formed, a compound of the formula L is produced, which may be subjected, if desired, to complete or partial hydrogenation of the unsaturated alkyl group R_9.

According to this second method compounds may be produced, which contain not only a 17-(β) OH-group, but also a group

$$-C\equiv CH, \quad -CH=CH_2, \quad -CH_2-CH_3,$$

$$-C\equiv C-CH_3, \quad -CH=CH-CH_3, \quad -CH_2-CH_2-CH_3$$

at the position 17.

In the two methods it must be considered that under certain circumstances reactions at the carbon atom 3 may take place, if a keto group is bound thereto.

This keto group may be "protected" by conversion into an ether, an enamine or a glycolacetal. To this end methods are known described in American Patent Specification 2,774,777, German Patent Specification 954,695 and Swiss Patent Specification 235,484. If not only a 3-keto group but also an unsaturated double bond prevails between the groups 4 and 5, it is advisable during ethynilation at the carbon atom 17 to use two mols of alkali metal in the presence of at least two mols of acetone, at a temperature below $-40°$ C., preferably below $-60°$ C. as described in German Patent 1,016,707.

When using the Grignard method protection of any 3-keto group is not required, if the reaction is carried out with equimolar quantities of the Grignard compounds.

It should be noted that during the production by the two methods, the saturated or the unsaturated aliphatic radical arrives at the α position and the 17-hydroxy group in β configuration.

The reactions described in this Chapter are preferably carried out with those compounds in which R_1 to R_8 and R_{11} have the meanings mentioned in the first part of Chapter I.

The reactions of this chapter are particularly explained in Examples 4, 5, 6 and 7 and 11 for the production of compounds of the formulae XVII, XVIII, XIX and XXII.

Chapter VII.

For the preparation of those compounds according to the invention which in the 17-position have a hydroxy or an etherified or esterified hydroxy group and furthermore an acetyl group, the following should be pointed out.

The starting material preferably is a compound having the general formula J, in which Q^{VI} is a methyl group and Q^{VII} an aldehyde group. The preparation of compounds of this group is described in Chapter IV.

Subsequently, the starting materials are subjected to oxidation to form compounds having the formula M, after which these epoxyformates are hydrolysed to form compounds having the formula N according to a method described in J. Am. Chem. Soc. 79, pages 456 seq. q. (1957). According to this method, the oxidation is performed with a peracid, for example with monoperphthalic acid. Other suitable peracids are peracetic acid and perbenzoic acid. The oxidation can be effected at a temperature between 0° C. and 40° C. Very good results were obtained at room temperature. Preferably, the reaction is performed in an inert solvent. Suitable solvents are, for example, ethyl acetate, benzene, chloroform, tetrachloromethane, toluene, petroleum ether, methyl acetate. The dura-

tion of the reaction is from 10 minutes to 24 hours according to the temperature. At room temperature the reaction is completed after approximately 16 hours. In this reaction, per mole of the initial material 2 moles of peracid are consumed while some of the peracid is decomposed during the reaction. Hence, it is of importance to use from 2 to 3 moles of peracid for each mole of the initial material. After decomposition of any excess of peracid, the formed (ep)oxidation product is hydrolysed. This may be effected both in alkaline and in acid conditions. The latter is preferred in order to avoid the formation of D-homosteroids. In the case of alkaline hydrolysis, this side reaction can be prevented by using mild reaction conditions, for example, room temperature and hydrolysis with dilute alcoholic aqueous solution of caustic soda.

The esterification of the 17-hydroxy group can be performed, after isolation of the compound concerned, with an excess for (example 30 times the equivalent amount) of the anhydride or, as the case may be, equivalent amounts of acid chloride of the acid desired. If required, in the esterification a catalyst, for example paratoluene sulphonic acid, is used. The esterification is preferably carried out under mild conditions, that is to say, at a temperature of from 10° C. to 30° C. and with the use of a solvent, for example acetic acid, in order to avoid the formation of D-homo-compounds.

The 3-enol esters can be produced in the esterification of the 17-hydroxy group and especially if the esterification is effected with a large excess (for example at least 100 times the equivalent amount) and without the use of a diluent of the acid anhydride or the acid chloride. In both cases, the reaction takes a comparatively long time, that is to say, from about 10 to 30 hours. The 3-enol-17-hydroxy-diester which may be produced, can, if required, be saponified under the action of dilute acids, for example a dilute solution of HCl or H_2SO_4 in methanol or ethanol, to form the 3-keto-17-hydroxy-monoester.

The method described above can be applied to the starting materials having the formula J for which Q^{VI}, Q^{VII} and X have the above-mentioned meanings.

This method is particularly suitable for those starting materials in which, in the group X, R_1 to R_6 and R_{11} have the meaning of Chapter I, first paragraph and first sentence of the second paragraph.

It should be noted that, for the preparation of the compounds in accordance with the invention which contain *inter alia* a 3-keto group, a $\Delta^{4,6}$ unsaturated system, a 17-hydroxy group which may be etherified but preferably is esterified, and a 17-acetyl group, as starting materials use can be made of the compounds which contain a 3-keto, 17-hydroxy and (if required, etherified or esterified) 17-acetyl group and a Δ^4 double bond but no Δ^6 double bond. In these compounds, the Δ^6 double bond can readily be introduced by dehydrogenation with chloranil (tetrachlorobenzoquinone). In this connection, we refer to the discussion of the preparation of compounds containing a $\Delta^{4,6}$ system in Chapter VIII of this application.

Details of the methods described in this chapter are found in the Examples 16 to 23 for the preparation of compounds having the formulas XXXII to XXXVIII.

CHAPTER VIII.

For the preparation of that group of compounds in accordance with the invention which is indicated in Formula Y_2, where R_2, R_3, R_7, R_8, R_9, R_{10} and R_{11} have the meanings mentioned hereinbefore in the definition of the invention, and R_6 can represent not only the double bond present at 4 and 6-positions, but also a double bond in at least one of the positions 1, 15 and 16, and R_5 and R_6 have the meaning mentioned, hereinbefore but not a halogen atom, suitable starting materials are compounds having the formula Y_1, in which R_1, R_3, R_5 to R_{11} have the same meanings as in the Formula Y_2 and R_2 likewise has the same meaning but cannot represent a Δ^6 double bond, compounds of the Formula Y_1 are subjected to selective 6-dehydrogenation. There are several suitable methods. According to one method, a compound having the Formula Y_1 is subjected to halogenation with a halogenating agent capable of introducing a halogen atom at the allyl position of a double bond. A suitable halogenating agent is, for example, N-bromo-succinimide. By subsequent dehydrohalogenation, for example with an acid binder, preferably an organic base such a tertiary amine, for example an organic base such as pyridine, collidine, dimethylaniline, or an inorganic basically reacting compound, for example calcium oxide or calcium carbonate, if desired in the presence of a suitable solvent, the desired 3-keto-$\Delta^{4,6}$ compound of the Formula Y_2 is produced.

In another method, direct dehydrogenation with chloranil (tetrachlorobenzoquinone) is used. This method is very attractive. It is preferably carried out in a solvent. Suitable solvents are, for example, aromatic hydrocarbons, such as benzene, toluene, xylene, aliphatic hydrocarbons, such as ligroin, petroleum, lower aliphatic alcohols, such as ethanol, propanol, propanol-2, butanol, butanol-2, tertiary butanol and tertiary amyl alcohol. Preferably use is made of the solvents of which the boiling point exceeds 80° C. in order to enable the use of the highest possible reaction temperature and the highest possible reaction velocity. A very suitable reaction temperature lies between 100° C. and 150° C. In order

to prevent the formation of by-dehydrogenation products, it is desirable not to use an excess of chloranil or no large excess thereof.

The reactions described in this Chapter can be carried out very suitably with those compounds having the formula Y_2 for which R_1 to R_9 and R_{11} have the meaning given in this chapter, R_{10} is a hydrogen atom or a hydroxy group which may be etherified or esterified and R_{11} is one of the groups —CH(CH$_3$)—CHO, —CO—CH$_3$, —COCH$_2$O-acyl, methyl-, ethinyl-, ethylidene-, ethyl-, —CO—CH$_2$OH. Particularly suitable starting materials are those compounds having the Formula Y_1 for which R_1, R_2, R_3, R_4, R_7, R_8 and R_{11} represent hydrogen atoms and R_2 is not only the double bond in the 4-position but also no other, or one double bond in the 1-position. Here also, R_9 and R_{10} have the meaning given in the preceding paragraph.

The methods described in this chapter are described more fully in the Examples 8, 15a, 21, 22 and 23 for the preparation of compounds having the Formulas XX, XXVII, XXXVII, and XXXVIII.

Chapter IX.

Suitable starting materials for the preparation of that group of compounds in accordance with the invention, which is indicated by the Formula Z_3 are compounds of the Formula Z_2.

The compounds having the Formula Z_2 can be prepared from compounds having the Formula Z_1.

Compounds having the formula Z_1 can also be converted to compounds having the Formula Z_3 by means of a reaction with lead tetra-acetate or by microbiological hydroxylation, followed if required by etherification or esterification of any free 21-hydroxy group formed.

In these formulae, R_1 to R_4 and R_{10} and R_{11} have the meanings mentioned hereinbefore in the definition of the invention, while Hlg is a halogen atom and R_{12} is a hydroxy or an etherified or esterified hydroxy group.

The conversion of compounds having the Formula Z_1 to compounds having the Formula Z_2 may be effected, by condensation under anhydrous conditions with a dialkyl ester of oxalic acid in the presence of an alkali-metal alkoxide in a solvent. If the steroid skeleton at the 3-position has a keto group, and if in the allyl-position with respect to this keto group substitution can take place, this reaction is preferably performed with equimolar amounts of dialkyl oxalic ester. Suitable alkyl esters of oxalic acid are, for example, the dimethyl- and diethyl-esters. Suitable alkali metal alkoxides are, for example, sodium or potassium methoxide or ethoxide. Suitable solvents are, for example, aromatic and aliphatic hydrocarbons and lower aliphatic alcohols or mixtures of these substances, for example, petroleum ether, benzene, ligroin, toluene, xylene, methanol and ethanol. The temperature of the reaction preferably lies between 15° C. and the boiling temperature of the reaction mixture.

The compounds produced (Formula Z_{10}) can be converted to compounds having the Formula Z_3 by the action of molecular halogen, preferably bromine or iodine, in the presence of a solvent, preferably a lower aliphatic alcohol for example methanol or ethanol. The temperature of the reaction is preferably kept between −80° C. and +10° C. A temperature between −10° C. and −20° C. has proved very suitable. The reaction product obtained can be decomposed for example with an alkali metal alkoxide, for example, with sodium methoxide in a solvent, for example methanol, to produce a compound having the Formula Z_2.

The conversion of a compound having the formula Z_2 into a compound of the Formula Z_3 is effected by acylation. A suitable reaction is a reaction under anhydrous conditions with an alkali or an alkaline earth salt of an organic carboxylic acid preferably as a dispersion, for example the K or the Na salts of one of the carboxylic acids mentioned in the Examples 7, 10, 20 and 23. In this reaction, compounds are produced which have the Formula Z_3 and for which R_{12} is an esterified hydroxy group. This group can be converted to a hydroxy group in the normal manner by saponification and this hydroxy group can, if required, be converted to the corresponding etherified hydroxy groups by etherification.

The reaction described in this chapter is of particular importance with respect to those compounds of the Formulas Z_1 and Z_2 for which R_1 is hydrogen, R_2 is a double bond in at least one of the positions 1, 4, 6 or 16, R_3 is a methyl group or a hydrogen atom, R_4 is a keto group or a hydroxy group which may have been esterified or etherified in the manner described in the Examples 7, 10, 20 and 23, R_5 is a hydrogen atom, R_6 is a hydroxy group which may be etherified or esterified in the manner described in the Examples 7, 10, 20 and 23 or a chlorine or fluorine atom or a hydrogen atom, R_7 is a hydrogen atom or a fluorine atom, R_8 is a keto- or a hydroxy group or a hydrogen atom, R_{10} is a hydrogen atom or a hydroxy group which may be etherified or esterified as described in one of the Examples 7, 10, 20 or 23, and R_{11} is a hydrogen atom, a methyl group or a hydroxy group which may be etherified or esterified in the manner described in the Examples 7, 10, 20 or 23.

The method described in this Chapter is described more fully in the Examples 2a, 2b and 2c for the preparation of compounds having the Formulas IX, X and XI.

Chapter X

For the production of that group of compounds according to the invention which is indicated by the formula S_2, wherein R_1, R_2, R_3, R_4, R_7, R_8, R_9, R_{10} and R_{11} have the meanings indicated in the definition of the invention, and R_6 can be not only the already available double bond at the position 1 but also a double bond at one or more of the positions 4, 5, 6, 15 and 16, the starting material may be compounds of the formula S_1, wherein R_1, R_2, R_5 to R_{11} have the same meanings as in formula S_2 and R_6 also has the same meaning, but cannot be a double bond at the position 1, by subjecting compounds of the formula S_1 to selective Δ^1-dehydrogenation and, if desired, by converting the compounds obtained of the general formula S_2 into their functional derivatives. To this end various methods may be used.

In one method the double bond at the position 1 of the compounds of the Formula S_1 is introduced by halogenation of these compounds at the position 2, followed by elimination of hydrogen halide.

According to a further method the introduction of the double bond into the compounds of the formula S_1 takes place by direct biochemical dehydrogenation. In a further method direct dehydrogenation at the position 1 of the compounds of the formula S_1 takes place by treating these compounds with iodine pentoxide or iodic acid or with a compound capable of producing, during the reaction iodine pentoxide or iodic acid.

A very suitable method is that in which direct dehydrogenation of the single bond at the position 1 is obtained by treating compounds of the formula S_1 with selenium dioxide or selenic acid. This dehydrogenation takes place preferably in an aqueous or a non-aqueous organic solvent such as a lower aliphatic alcohol. Preferably the reaction is carried out in the presence of a tertiary alcohol, for instance tertiary butanol or tertiary amyl alcohol. Suitable solvents may be, for instance, if desired mixed with one of the aforesaid tertiary alcohols, lower primary and secondary aliphatic alcohols, for example methanol, ethanol, propanol, isopropanol, ethyleneglycol, aliphatic or aromatic hydrocarbons, for instance, hexane or benzene, aliphatic or aromatic ethers, such as ethylether, dibutylether, or anisole. Use may furthermore be made, as solvent, of carbon tetrachloride, pyridine, ethylacetate and acetonitrile or mixtures of all these solvents.

The reaction may be accelerated by adding an inorganic or organic acid, preferably an aliphatic carboxylic acid such as acetic acid, propionic acid or benzoic acid. Some of these organic acids, for example, acetic acid and propionic acid may serve at the same time as a solvent for the reaction constituents. If the reaction is carried out in the presence of water or a solvent mixable with water, for example alcohol, the addition of an acid differing from H_2SeO_3 is not absolutely necessary for the acceleration of the reaction.

The reaction takes place preferably at a temperature between room temperature and the boiling point of the reaction mixture, preferably at the exclusion of oxygen, for example, under nitrogen.

In general use is made of the quantity of selenium dioxide calculated for the introduction of a double bond. However, if an excess quantity of selenium dioxide is added, this excess quantity is decomposed at the termination of the reaction with a reducing agent, for example, sulphur dioxide or lead acetate.

The reaction described in this chapter may be very suitably carried out with those compounds of the formula S_1 in which R_1 to R_6 and T_{11} have the meanings referred to in this chapter, R_{10} is a hydrogen atom or a hydroxy group which may be etherized or esterified, and R_9 is one of the groups —CH(CH$_3$).CHO, —CO—CH$_3$, CO—CH$_2$—O-acyl, methyl-, ethinyl-, ethylidene-, ethyl-, —CO—CH$_2$OH. Particularly suitable starting substances are those compounds of the formula S_1 in which R_1, R_2, R_3, R_6, R_7, R_8 and R_{11} are hydrogen atoms, R_6 is a single or a double bond at the position 4 or double bonds at the positions 4 and 6, R_9 and R_{10} have also the meanings indicated in the preceding paragraph.

The methods described in this chapter are explained in Example 13 for the production of the compound of the formula XXIV.

Chapter XI.

For the production of that group of compounds according to the invention indicated by the formula T_2, wherein R_1, R_2, R_6, R_7, R_8, R_9, R_{10} and R_{11} have the meanings indicated in the definition of the invention and R_6 may be a double bond at one or more of the positions 4, 5, 6, 15 and/or 16, whilst Alk is a methyl- or an ethyl-group, the starting material may be compounds of the formula T_1, wherein R_1 to R_{11} have the same meanings as in the formula T_2, the production being carried out by condensing compounds of the formula T_1 with a dialkyl ester of oxalic acid such as the dimethyl or diethyl ester in the presence of a condensing agent, products being obtained of the formula T_3, wherein R_1 to R_{11} have the same meanings as in the formula T_2 and R_{12} is an alkyl group.

The compounds of the formula T_3 are then caused to react with a methyl- or ethylhalide and the compounds mentioned herein are finally subjected to a treatment with an alkali metal alkoxide, compounds of the formula T_2 being thus obtained.

The conversion of the compounds of the formula T_1 into compounds of the formula T_2 is preferably carried out in anhydrous conditions with esters of lower aliphatic alco-

hols, for instance, methanol, ethanol, propanol, of oxalic acid.

Suitable condensing agents for this reaction are, for instance, alkali metal hydrides such as sodium hydride or an alkali metal alkoxide such as sodium methylate. The reaction is preferably carried out in the presence of a solvent. Suitable solvents in this case are, for instance, lower aliphatic alcohols, such as tertiary butylalcohol or aromatic or aliphatic hydrocarbons such as benzene or ligroin.

The reaction takes place preferably at a temperature between 10° C. and the boiling point at the reaction mixture.

After the conversion of the alkali metal enolates obtained for example with the aid of an acid, compounds of the formula T_2 are obtained.

The reaction of the compounds of the formula T_2 with methyl-or ethylhalide is preferably carried out with iodides or bromides. If desired, a solvent may be added to the reaction mixture, use may be made for example, of aliphatic ketones such as acetone or methyl-ethylketone. To the reaction mixture is preferably added a condensing agent such as an alkali metal carbonate, or an alkali metal bicarbonate such as potassium carbonate or sodium bicarbonate. The reaction takes place preferably at a temperature between room temperature and the boiling temperature of the reaction mixture. The reaction duration may vary strongly in accordance with the reaction temperature, for example, between half an hour and 45 hours.

The reaction products obtained can be subjected, in order to obtain compounds of the formula T_3, to a reaction with an alkali metal alkoxide, under anhydrous conditions. Suitable alkali metal alkoxides are, for instance, the Na-, K- or Li-compounds of lower aliphatic alcohols, for example, methanol, ethanol, propanol or tertiary butylalcohols.

Also this reaction is preferably carried in anhydrous conditions in a solvent. Suitable solvents are, for instance, lower aliphatic alcohols, for example, methanol, ethanol, propanol or tertiary butanol. The reaction temperature is preferably chosen to lie between 10° C. and the boiling temperature of the reaction mixture.

The reactions described in this chapter may be suitably carried out with those compounds of the formula T_1 wherein R_1 to R_4 and R_{11} have the meanings indicated in this chapter, R_{10} is a hydrogen atom or a hydroxy group which may be etherified or esterified, and R_9 is one of the groups:

—$CH(CH_3)$—CHO, —CO—CH_3, —CO—CH_2O-acyl, methyl-, ethinyl-, ethylidene-, ethyl- or —CO—CH_2OH.

Particularly suitable starting subsequences are those compounds of the formula T_1 wherein R_1, R_3, R_6, R_7, R_8 and R_{11} are hydrogen atoms, R_2 is a single bond or a double bond at the position 4, or double bonds at the positions 4 and 6 or 4 and 7. R_9 and R_{10} have also in this case the meanings indicated in the preceding paragraph.

The methods described in this chapter are set out in the Examples 14a and 14b for the production of the compounds of the formula XXV and XXVI respectively.

One or more of the biologically active compounds in accordance with the invention can be worked into pharmaceutical preparations in the conventional manner, for example, mixed with or dissolved or dispersed in a solid or liquid excipient. If the compounds are orally active, they can be worked into tablets or dragés in the usual manner. For example, tablets of 200 mgs are made which contain from 1 to 10 mgs of active ingredient and furthermore a vehicle, for example lactose or starch, and a lubricant, talc and/or magnesium stearate, and, if required, flavouring or colouring matter.

For the preparation of injection liquids, the active compounds can be dissolved or dispersed in water, if required with the addition of a buffer, a solubility promoter or a dispersing agent.

EXAMPLE 1A

By very vigorously stirring 125 gs of $\Delta^{4,7,22}$-lumista-triene-3-one (Formula I) was dissolved at +10° C. in 2.2 litres of dry propanol-2, which had previously been saturated with dry hydrochloric acid gas. After another half hour of passing over a slow flow of hydrochloric acid gas, the liquid was decanted as rapidly as possible, whilst stirring, into a mixture of solid sodium bicarbonate and a saturated bicarbonate solution, obtained by stirring 4 kgs. of sodium bicarbonate, with 8 litres of water. After standing some time the yellowish isopropanol layer was separated off and the salt layer twice extracted with one litre of petroleum ether. The keto ether layers were then washed with a sodium bicarbonate solution and water (three times), then dried on sodium sulphate and evaporated to dryness after filtering. The ultraviolet absorption spectrum exhibited a maximum at 287 mμ, of which the $E\,\frac{1\%}{1\ cm}$ is 562 (content of pure substance about 85%).

The residue obtained was dissolved in 250 mls of boiling petroleum ether (40 to 60° C.) and crystallized at −5° C. for a few hours and finally by night at −25° C. Filtering yielded 80.5 gs of $\Delta^{4,6,22}$-lumistatriene-3-one (Formula II) with a melting point of 99 to 100.5° C. (yield good 64%). A portion of the substance was recrystallized several times with petroleum ether for analysis, the melting point rising to 101—102° C.

$(\alpha)_D^{25°} = -632°$ ($CHCl_3$). $\varepsilon(\lambda = 287\ m\mu) = 26200$

Found: C 85,67% H 10,65%
85.68% 10.77%
Calculated for $C_{25}H_{42}O$: 85.22% H 10.73%.

In the infrared spectrum were found apart from the 964 cm^{-1} band for the side chain trans-ethylene bond three characteristic bands at 1586, 1622 and 1661 cm^{-1}.

EXAMPLE 1B.

Whilst stirring vigorously, a solution of 3.0 gs of $\Delta^{4,6,22}$-lumistatriene-3-one (Formula II) in 300 mls of dry diethyl ether was added to 450 mls of liquid ammonia. During the addition of the first portion of the solution the liquid crystallized out, but was again dissolved after a larger portion had been added. Then, whilst vigorously stirring, a solution of 420 mgs of lithium in 100 mls of ammonia was carefully added in drops, until no spontaneous decolouring occurred any more. After dripping in 90 mls of dry ethanol, stirring was continued for 30 minutes, the mixture was diluted with water and the reduction product was dissolved in diethyl ether. The ethereal extracts were thoroughly washed with water, dried on Na_2SO_4, filtered and evaporated to dryness, a light-yellow resin being obtained.

($E\ \frac{1\%}{1\ cm}$ (λ_{max} 242 $m\mu$) = 196).

The resin was dissolved in 100 mls of boiling ethanol and after the addition of 6 mls of 2N NaOH boiled for five minutes, after which cooling was performed rapidly. By diluting with water, extracting with diethylether, washing the ethereal layers with water, drying, filtering and evaporating to dryness, a light-brown, completely solid residue was finally obtained with $E\ \frac{1\%}{1\ cm}$ (λ_{max} 242 $m\mu$) = 420.

This substance was chromatographed in 24 mls of pure benzene on 30 gs of Al_2O_3 (III) and eluted with the same solvent (total 75 mls), a dark brown ring remaining at the upper end of the column. The dry eluate was recrystallized with 45 mls of methanol at +5° C., after which the filtered product was washed with 20 mls of methanol of −24° C. The yield were long light-brown needles (1.5 to 2 cms in length) weight 2.43 gs and melting point 122 to 124° C.

500 mgs of the substance were recrystallized twice with 3 mls of acetone at −5° C., after which finally 313 mgs of colourless crystals of $\Delta^{4,22}$-lumistadiene-3-one was obtained (Formula III).

$E(\lambda\ 242 m\mu) = 16.800$, melting point 122—124° C.
$(\alpha)_D^{20} = -125°$ ($CHCl_3$)

Found: C 84.98% H 10.96%
C 84.89% H 11.03%
Calculated for $C_{25}H_{44}O$= C 84.79% H 11.17%

In the infrared spectrum an intensity band was found at 1665 cm^{-1}, a slightly weaker band at 1620 cm^{-1}, a weak band at 962 cm^{-1} and a slightly more intense band at 978 cm^{-1}.

In a mixture of 750 mls of freshly distilled methylene chloride and 5.75 mls of dry pyridine, 20 gs of $\Delta^{4,22}$-lumistadiene-3-one (Formula III) was dissolved and the mixture, whilst stirring magnetically at −80° C. (hydrocarbon ice acetone freezing mixture) ozonized for 4 hours and a half. (0.205 mol ozone min), speed of passing oxygen (=VO_2)=9 to 10 l/hour). The ozonide formed was then decomposed at 0° C. for one hour by stirring it with a suspension of 20 gs of zinc dust, after the addition of 105 mls of glacial acetic acid. The reaction mixture was then warmed for 5 minutes at 35° C. and then the solid substance was separated out by filtering. After the addition of ice the filtrate was washed successively with 75 mls and 50 mls of ice-cold 10% Na_2CO_3-solution, 50 mls of 10% NaOH solution of 0° C. and 4×300 mls of icewater.

The methylene chloride layer was then dried on Na_2SO_4, filtered and the filtrate was distilled to dryness, the last part of which was carried out in vacuo. The colourless, practically completely crystalline residue was recrystallized with 50 mls of diethyl ether at −25° C., the first crystallate being 10.1 gs of 3-keto-lumi-bis-nor-chol-4-en-22-al of the formula IV (of the lumisterol series) with a melting point of 119 to 121° C. Repeated recrystallisation with petroleum ether (boiling range 40 to 60° C.), to which a few drops of ethylalcohol had been added, and with diethyl ether, raised the melting point to 122—123° C.

The further analytic data of the pure substance were:—

$E(\lambda_{max}\ 242.5\ m\mu) = 16,700$ $(\alpha)_D^{23} = -144°$ C. ($CHCl_3$)
Found: C 79.87% H 9.73%
C 80.06% H 9.81%
Calculated for $C_{22}H_{32}O_2$: C 80.42% H 9.82%

The infrared spectrum exhibited characteristic bands at 1712, 1642 and 1610 cm^{-1}.

EXAMPLE 1c.

A solution of 450 mgs of aldehyde, obtained as described in Example 1b (Formula IV) in 15 mls of chloroform and 25 mls of acetic acid, was oxidized at about 30° C. for 16 hours by means of 200 mgs of chromic acid and 0.2 mls of water dissolved in the mixture.

After the excess of chromic acid had been decomposed by stirring for 30 minutes with 1.5 mls of methanol, the mixture was diluted with water and the product precipitated was dissolved in benzene. The benzene extract was washed with water to neutral reaction, dried on Na_2SO_4 and filtered. After evaporation to dryness a crystalline residue was obtained, which, by crystallisation with diethyl ether, yielded 340 mgs of 3-keto-lumi-bis-nor-chol-4-ene-acid (Formula V), melting point 194 to 198° C. Several recrystallisations raised the melting point to 202 to 204° C.

$E(\lambda_{max}\ 242\ m\mu)=16800$

Calculated for $C_{22}H_{32}O_2$: C 76.70% H 9.36%
Found: C 76.93% H 9.45%
C 76.92% H 9.48%

EXAMPLE 1d.

A solution of 450 mgs of ozonide in 25 mls of methylene-chloride obtained in the manner described in Example 1b, by ozonizing $\Delta^{4,22}$-lumistadiene-3-one, was oxidized with a solution of 200 mgs of chromic acid in 25 mls of acetic acid overnight at 30° C. The excess quantity of chromic acid was then decomposed by stirring with 2 mls of methanol for 30 minutes. After dilution with water the mixture was dissolved in diethyl ether and the ether-methylene chloride extract was extracted three times with 50 mls of 2% of NaOH. These aqueous layers were combined, and washed with diethyl ether to remove residues of neutral constituents. The free organic acid was liberated by acidifying with concentrated hydrochloric acid and extrated with diethylether. After neutral washing with water, the mixture was dried on Na_2SO_4, filtered and finally evaporated to dryness, the yield was 240 mgs of crystalline residue. A crystallisation with methanol at −5° C. yielded 150 mgs of 3-keto-lumi-bis-nor-chol-4-ene-acid (Formula V) with a melting point of 200 to 203° C.

The substance obtained did not exhibit a drop in melting point during mixture with a substance obtained by Example 1c.

EXAMPLE 1e

A solution of 300 mgs of the aldehyde (Formula IV) obtained by ozonization of $\Delta^{4,22}$-lumistadiene-3-one, was heated in 5 mls of dry benzene, after the addition of 0.11 mls of dry, freshly distilled piperidine and 1 to 5 mgs of *p*-toluene-sulphonic acid, for 3 hours under N_2 under reflux, the refluxing benzene being dripped, to remove the water formed, through powdered BaO in an extraction column.

After cooling the reaction mixture was poured out in water, dissolved in diethyl ether and then washed adequately four times with water. The ether-benzene layer dried on Na_2SO_4 and filtered was dried to complete dryness in vacuo. The resinous residue was stirred at −15° C. with 3 mls of methanol and, after recrystallisation, cooled at −25° C. for 2 hours. Filtering yielded 185 mgs of needles with a melting point of 88 to 93° C. of a compound of Formula VI, i.e. $\Delta^{4,20(22)}$-22-(N - piperidino) - lumi-bis-nor-choladiene-3-one.

Two recrystallisations with methanol raised the melting point to 94—96° C.

$E(\lambda_{max}\ 241.5\ m\mu)=21.800$
$(\alpha)_D^{20}=-139°\ (CHCl_3)$

Found: C 81.72% H 10.64% N 3.60%
C 81.78% H 10.67% N 3.66%
Calculated for $C_{27}H_{41}NO$: C 81.97% H 10.45% N 3.54%

The infrared spectrum exhibited an intensive band at 1660 cm^{-1}, which overlapped distinctly a band with lower extinction at 1650 cm^{-1}. Apart from a band at 1610 cm^{-1} a weaker band was found at 874 cm^{-1}. After a few small charges of enamine were produced in a similar manner, in which the final substance had a melting point of 94 to 95° C., the production on a large scale was started. An enamine with a different melting point (114 to 115° C.) was obtained in large quantities. Probably this is due to cis-trans isomers.

A solution of 10 mgs of the aldehyde according to Formula IV was boiled in 180 mls of dry benzene with 3.8 mls of piperidine and 30 mgs of *p*-toluenesulphonic acid for 3 hours under nitrogen under reflux. The refluxing liquid was dried through powdered barium oxide. The reaction mixture was then dried to complete dryness in vacuo, a crystalline residue of 12.3 gs being obtained, which, after

recrystallisation with 10 mls of methanol, yielded 9.3 gs of enamine of the Formula VI, melting point 98 to 107—111° C. A portion of the substance, which was adequately pure for further processing, was recrystallized several times with acetone for analysis until a constant melting point of 114—115° C. was attained.

The further analysis data found were:—

$E(\lambda_{max}$ 241.5 $m\mu)=22{,}000$

$(\alpha)_D^{23}=-123°$ ($CHCl_3$)

C 81.87% H 10.49% N 3.42%

C 81.98% H 10.47% N 3.63%

The infrared spectrum of this substance differed only on details from that of the preparation having a melting point of 94 to 96° C. the characteristic bands found for the said substance were also found in this case.

EXAMPLE 1F

To a solution of 1 g of aldehyde (Formula IV) obtained as described in Example 1d, in 50 mls of freshly distilled acetic acid anhydride was added 0.5 g of freshly melted Na-acetate and the mixture was refluxed in a nitrogen atmosphere.

Then the solvent was distilled off as far as possible under reduced pressure (about 10 minutes) and the residue obtained was dissolved in 25 mls of chloroform. The non-dissolved Na-acetate was filtered off, the filter was washed with a small quantity of chloroform and the filtrate was completed with the same solvent to 125 mls, a solution of the compound according to Formula VII being obtained, i.e. $\Delta^{4,20(22)}$-lumi-bis-nor-choladiene-3-one-22-O-acetate.

EXAMPLE 1G

A solution of 300 mgs of enamine (Formula VI) (piperidino-) of the aldehyde, obtained by ozonization of $\Delta^{4,22}$-lumistadiene-3-one in 4.5 mls of dry thiophene-free benzene, was added in drops at −5° C.—+5° C., whilst stirring, during 45 minutes, to a solution of 453 mgs of sodium bichromate (2 aq) in 4.5 mls of acetic acid and 3 mls of benzene. After stirring for 2 hours at 0° C., 0.75 ml of methanol was added to the dark-coloured solution and at the same temperature stirring was continued for 30 minutes.

The reaction mixture was processed by pouring it out in 25 mls of water and extraction with benzene. The saturated benzene extracts were then washed with water, 3 mls of cold 10% NaOH solution (twice) water, 3 mls of cold 10% hydrochloric acid solution and water (four times). From the solution dried on Na_2SO_4, filtered and evaporated to dryness was finally obtained a completely crystalline residue.

This was dissolved in 1 ml of methylene chloride and 4 mls of petroleum ether was added at boiling temperature. The crystallisation completed at −25° C. yielded 150 mgs of light-yellow, hard crystal blocks with a melting point of 161 to 163° C. (lumiprogresterone) (Formula VIII). A repeated recrystallization yielded 130 mgs with a melting point of 163—164° C.

$E(\lambda_{max}$ 241.5 $m\mu)=16{,}800$. $(\alpha)_D^{20}=62°$ ($CHCl_3$)

Found: C 79.90% H 9.75%

C 79.89% H 9.75%

Calculated for $C_{21}H_{30}O_2$: C 80.20% H 9.26%

The infrared spectrum exhibited strong bands at 1690 cm^{-1} and 1662 cm^{-1} and a weaker band at 1615 cm^{-1}.

EXAMPLE 1H

To a solution of 1 g of aldehyde (Formula IV), (obtained as described in Example 1b) in 50 mls of freshly distilled acetic anhydride was added 0.5 gs of freshly melted Na-acetate and the mixture refluxed for 16 hours in a nitrogen atmosphere.

Then the solvent was distilled off as far as possible under reduced pressure (about 10 mm Hg) and the residue obtained was dissolved in 25 mls of chloroform. The non-dissolved Na-acetate was filtered off, the filter was washed again with a small quantity of chloroform and the filtrate was completed with the same solvent to 150 mls. A solution of the compound of Formula VII was obtained.

Under cooling with ice water the solution was ozonized for 14 minutes, 10.5 mgs of ozone being absorbed per minute. Then, after the addition of 15 mls of acetic acid and 2 gs of zinc substance for 10 minutes the mixture was shaken and after filtering the solution was washed with 10% NaOH, solution and water (to neutral reaction). The solution dried on Na_2SO_4, filtered and evaporated to dryness, was then refluxed for hydrolisation of any 3-enolacetate, for 45 minutes in 45 mls of methanol and 25 mls of $(NH_4)_2SO_4$. After concentration *in vacuo* down to half the volume the organic substance was dissolved in diethyl ether and the ethereal extract was washed with 10% NaOH solution and water (to neutral reaction), dried on Na_2SO_4, evaporated to dryness and finally crystallized with 3 mls of diethyl ether. The crystallate obtained was recrystallised with a mixture of methylene chloride and *n*-hexane, the yield being 113 mgs of substance with a melting point of 160—163° C. The substance did not exhibit a reduction in melting point with the lumiprogesterone obtained as described in Example 1g.

$(\alpha)_D^{20}=-61.5$ C. ($CHCl_3$) (mean value of −62.1° and −60.9°).

EXAMPLE 2A

In a mixture of 70 mls of dry benzene and 12 mls of 2.86 Na-methoxide in dry methanol was introduced 3.2 mls of anhydrous ethanol and the mixture was concentrated under N_2 to about 30 mls. After cooling, whilst stirring, the paste had added to it, 8.6 mls of freshly distilled diethyl-oxalate, so that the reaction mixture became quite clear. A solution of 10 gs of lumiprogesterone (Formula VIII), prepared as described in Example 1 g, in 70 mls of dry benzene was then added all at once and stirring was continued for about 90 minutes. By dripping in rapidly 400 mls of dry diethylether the precipitate of the Na-enolate was completed. After stirring in addition for 45 minutes the substance was filtered and washed adequately with 100 mls of dry diethylether; after drying, for 15 hours, on concentrated H_2SO_4, 10.8 gs of yellow Na-enolate of 21-ethoxy-oxalyl-lumi-progesterone (Formula IX) was obtained.

EXAMPLE 2B

The Na-elonate thus obtained was dissolved at −20° C., whilst stirring, in a nitrogen atmosphere, in 150 mls of dry methanol. At the same temperature, whilst stirring, a solution of 5.9 gs of iodine in 210 mls of dry methanol was added within 14 minutes to the reaction mixture and stirring was continued for 90 minutes. The decomposition of the iodine compound was carried out by adding 6.6 mls of 3.56 N Na-methoxide solution in dry methanol and then, at 0° C., for one hour, stirring was continued. From the solution obtained the reaction product was precipitated by dripping in whilst stirring, during 45 minutes, 90 mls of water and by adding subsequently 120 gs of sodium chloride.

The filtered deposit, after washing adequately with water, was dried for one night, the yield being 5.55 gs of 21-iodine-lumiprogesterone (Formula X). From the filtrate, after one night, another 2.35 gs was obtained.

EXAMPLE 2C

The first fraction of 21-iodo-lumiprogesterone (weight 5.55 gs) obtained in this way, was refluxed in 200 mls of purified, dry acetone (purified by $KMnO_4$ and K_2CO_3) for 18 hours with 12 gs of freshly melted potassium acetate. After evaporation of the acetone 300 mls of water was added and the oil separated was dissolved in methylene chloride. The extract, after drying on Na_2SO_4, was evaporated to dryness (weight 1.4 gs) and chromatographed in benzene on 10 gs of neutralized Al_2O_3. Elution with benzene yielded 700 mgs of residue, from which after recrystallisation with acetone, 150 mgs of substance with a melting point of 159 to 164° C. was obtained.

Corresponding acetylation of the second-fraction obtained in Example 2b of 21-iodo-lumiprogesterone (2.35 gs) yielded 2.6 gs of crude acetoxy-compound, from which 90 mgs of solid substance with a melting point of 160—161° C. could be crystallized. Chomography of the mother lye as described above, followed by recrystallisation with acetone, plus petroleum ether (40—60° C.) yielded 400 mgs with a melting point of 160°—163° C.

Recrystallisation of the combined crystallates with acetone yielded 425 mgs with a melting point of 164—167° C., from which, by recrystallisation with ethanol, finally 335 mgs of lumi-desoxycorticosterone acetate with a melting point of 165—168° C. was obtained (Formula XI).

$E^{1\ cm}_{1\%}(\lambda_{max}=242\ m\mu)=457$ and 462 $E_{242m\mu}=17{,}100$

Calculated for $C_{23}H_{32}O_4$ (372.49): C 74.50% H 8.66%
Found: C 74.03% H 8.55%
C 74.27% H 8.77%

The infrared spectrum exhibited inter alia bands at 1226, 1609, 1663, 1724, and 1751 cm^{-1}.

EXAMPLE 3A

To 9.6 gs of enamine (Formula VI) (obtained as described in Example 1e), dissolved in 475 mls of methylene dichloride was added dropwise whilst stirring, at −55° C., in a nitrogen atmosphere, a solution of 4.08 gs of bromine in 50 mls of methylene chloride. After the addition of 47 mls of the solution the mixture assumed a light-brown-colour, after which the addition was stopped. Thus a compound of the Formula XII was obtained. After the reaction mixture had been cooled to 0° C., 60 mls of water was added and stirring was performed very vigorously at 20° C. for 2 hours. The methylene chloride layer was then separated off, washed twice with 100 mls of water, and dried on Na_2SO_4. The residue contained a compound as per Formula XIII. To the filtered solution was added 70 mls of dry pyridine and the methylene chloride was distilled off *in vacuo*, after which under N_2, for 60 minutes, at 70° C. and then for 30 minutes at 100° C. dehydrobromization was carried out. Distilling off the pyridine in vacuo yielded a residue which was dissolved in methylene dichloride and then washed successively with 2 N HCl, water (three times), 5% $NaCO_3$ solution and water (three times), after which the mixture was dried on Na_2SO_4, filtered and evaporated to dryness. Yield a light-brown crystalline residue with a melting point of 150 (s)—153—155° and $E^{1\%}_{1\ cm}$ ($\lambda_{max}=248$ mμ)=865.

Recrystallisation from 30 mols of acetone at −5° C. yielded 6 gs of 3-keto-lumi-bisnorchol-4-17(20)-di-ene-22-al (Formula XIV) with a melting point at 154 (s)—155—158° C. A small quantity was crystallized, in order to obtain a pure preparation for analysing purposes, three times with acetone and once with ethanol. The analysis values were as follows:—

Melting point 151 (s)—155—159° C. $[\alpha]_D^{23}=-138$ ($CHCl_3$) $E_{1\,cm}^{1\%}$ (λ_{max} 248 mμ)=945, 930 and 956.

Calculated for $C_{22}H_{30}O_2$: C 80.98% H 9.20%
Found: C 80.95% H 9.10%
C 80.93% H 9.26%

The infrared spectrum exhibited a strong band at 1665 cm^{-1}, a shoulder at 1710 cm^{-1} and a weak band at 1620 cm^{-1}. It is not imposible, in view of the non-sharply defined melting point, that a mixture of cis-trans isomers is obtained.

EXAMPLE 3B

Whilst stirring, at −20° C., 5 gs of powdered $\Delta^{17(20)}$-unsaturated aldehyde (Formula XIV) (obtained as described in Example 3a) was suspended in a solution of 8 gs of NaCn in 50 mls of absolute methanol. To this suspension was added at −20° C. dropwise within about 45 minutes, 7.1 mls of glacial acetic acid, after which within about 2 hours, the reaction temperature was raised from −20° C. to +5° C. The white paste obtained was kept at +5° C. for 40 hours, after which it was processed by pouring it out into 150 mls of methylene chloride at 0° C. and washing in succession with 75 and 4×25 mls of ice water and drying on Na_2SO_4 at −5° C. for one night.

A small portion of the filtered solution was evaporated to dryness. Of the practically colourless residue the N-content found was 4.20% (theoretic value 3.96%) and $E_{1\,cm}^{1\%}$ (λ_{max} 244 mμ)=535 (methanol) $E_{1\,cm}^{1\%}$ (λ_{max} 233 mμ)=516 (diethyl ether). The compound thus obtained has the Formula XV.

The remainder of the filtrate was ozonized at −80° C., whilst stirring, after 1.5 mls of dry pyridine had been added. The duration of the ozonization was 75 minutes (per 10 min. 2.16 mmol O_3), the speed of the gas being about 10 l/hour.

The reaction mixture was then decomposed by stirring it for 2 hours with 5 gs of zinc dust and 15 mls of glacial acetic acid, the temperature rising slowly to 20° C. The filtered solution was then washed with water (150 mls) and (twice 100 mls), 10% NaOH solution (twice 50 mls) water (twice), 10% HCl solution (50 mls) and water (three times), dried on Na_2SO_4 and after filtering, evaporated to dryness. A few recrystallisations with ethanol yielded 1.48 gs of Δ^4-lumi-androstenedione-3.17 (Formula XVI), melting point 153—155° C.

A portion of this crystallate was recrystallized for analysis purposes with 90% and 96% ethanol, melting point 154—156° C.

Calculated for $C_{19}H_{26}O_2$: C 79.68% H 9.15%
Found: C 78.93% H 9.24%
C 79.20% H 9.22%

$E_{1\,cm}^{1\%}$ (λ_{max} 240.5 mμ)=569

The infrared spectrum exhibited a strong band at 1735 cm^{-1}, and a strong band at 1665 cm^{-1}. Apart from a shoulder at 1655 cm^{-1} a low peak at 1608 cm^{-1} was found.

EXAMPLE 3C

To a solution of 7.7 gs of a compound according to Formula IV (obtained as described in Example 1b) in 100 mls of carbon-tetrachloride, in which 3 gs of powdered calcium carbonate had been suspended, was added, whilst stirring vigorously at room temperature, in a nitrogen atmosphere, 48 mls of a bromine solution in carbontetrachloride (0.515 mmol per ml). At this reaction a compound of the Formula XIII is obtained. During the addition in drops, which took 75 minutes, a brown deposit was formed in the reaction mixture. The mixture was then filtered and washed with methylene chloride, the organic portion of the deposit being thus dissolved. The filtrate was then washed in succession with $NaHCO_3$ solution (twice) and water (twice), dried on Na_2SO_4 and, after the addition of 25 mls of dry pyridine, on the solution fitted from the inorganic salt evaporated to dryness in vacuo until the final volume was about 20 mls. After 30 mls of pyridine had again been added, dehydrobromination was carried out by heating under nitrogen at 70° C., for 60 minutes and for another 30 minutes at 100° C.

The pyridine was distilled off, as far as possible, *in vacuo* from the dark-coloured

solution, crystallisation of pyridine HBr occurring. The organic constituent was dissolved in methylenedichloride and the solution obtained was successively washed with $2NH_2SO_4$ (twice) water, 5% $NaHCO_3$ solution (once) and water (once). The solution dried on Na_2SO_4 and filtered by means of a small quantity of carbon, was finally evaporated to dryness, 7.15 gs of crystalline residue being thus obtained.

$E\ {}^{1\%}_{1\ cm}$ (λ_{max} 246.5 mμ)=630.

The crude $\Delta^{17(20)}$-unsaturated compound (Formula XIV) was converted into the cyanhydrin (Formula XV) in the manner described in Example 3b. The methylene chloride solution thereof was ozonized in the manner described in Example 3b.

The resin finally obtained could not be crystallized without the need for further means. $E\ {}^{1\%}_{1\ cm}$ (λ_{max} 241 mμ)=310. For purification chromatography was therefore carried out in petroleum-ether-methylene chloride (3:2) on 100 gs Al_2O_3 (Brockman method II) and eluated with a mixture of the same solvents with increasing quantities of methylenechloride up to a ratio of 1:4.

The collected fractions were together crystallized with 7.5 mls of alcohol (90%) at −5° C., 680 mgs of substance with a melting point of 35 to 139° C. was obtained.

The filtrate was concentrated and crystallized at −25° C. The crystallate (640 mgs, melting point 135—145° C.) was then recrystallized with ethanol (90%), ethanol, (96%) and ethyl acetate at −5° C., 240 mgs of the substance with a melting point of 152—155° C. being obtained. The substance was found not to give a mixture-melting point reduction with the Δ^4-lumi-androstene-3,17-dione (Formula XVI) obtained as described in Example 3b.

Calculated for $C_{19}H_{30}O_2$: C 78.55% H 10.41%
Found: C 78.60% H 10.93%
C 78.78% H 11.17%

The infrared spectrum had more or less strong bands at 863, 1048, 1059, 1077, 1236, 1421, 1468 and 1663 cm^{-1}.

EXAMPLE 5

In the manner described in Example 41, 13 gs of Δ^4-androstene-3,17-dione, derived from lumisterol was reduced to the crude Δ^4-3,17-diol (Formula XVII). Yield a colourless resin with practically not any absorption in the ultraviolet region.

$E\ {}^{1\%}_{1\ cm}$ (λ_{max} 240 mμ)=5.

The resin was then dissolved in 60 mls of chloroform and shaken for 17 hours with 6 gs of freshly produced manganese dioxide. The solution obtained after filtering through Na_2SO_4 was evaporated to dryness and yielded 1.2 gs of crystalline residue with $E\ {}^{1\%}_{1\ cm}$ (λ_{max} 241 mμ) of 620 and melting point of 147—152° C.

Recrystallisation with 30 mls of diethylether at −25° C. yielded 780 mgs, melting point 154.5—155.5° C. Evaporation and processing of the filtrate yielded another 105 mgs, melting point 152—153.5° (at 151° C. sintering).

A small quantity was purified by recrystallisations with diethylether, at −25° C., to a constant melting point at 155—156° C.

$E\ {}^{1\%}_{1\ cm}$ (λ_{max} 242 mμ)=575. $[\alpha]_D^{23}=-154$ ($CHCl_3$)

Calculated for $C_{19}H_{28}O_2$: C 79.12% H 9.68%
Found: C 79.07% H 9.97%
C 79.23% H 9.78%

The infrared spectrum of the lumitestosterone (Formula XVIII) exhibited strong bands at 1055, 1063, 1660 and 3420 cm^{-1} and a weaker band at 1612 cm^{-1}.

EXAMPLE 6

To a solution of 500 mgs of lumitestosterone, obtained as described in Example 5, in 10 mls of dry, freshly distilled pyridine, was

EXAMPLE 4

To a solution of 1.13 gs of Δ^4-lumi-androstene-dione-3,17 (Formula XVI) obtained from lumisterol, in 20 mls of dry tetrahydrofurane a solution of 550 mgs of $LiAlH_4$ in 55 mls of tetrahydrofuran was added dropwise, whilst stirring, with ice cooling. The thick paste obtained was refluxed subsequently for one hour and, after cooling the excess quantity of $LiAlH_4$ was decomposed carefully with ethyl-acetate. After dilution with diethyl ether, the reaction mixture was washed with water (three times), dried on Na_2SO_4 and evaporated to dryness. The reduction product was crystallized from a mixture of acetone-hexane at −5° C. Yield 0.6 gs of substance with a melting point 108—112° C. During the melting gas was developed, probably due to crystal solvent. After two recrystallisations with dry petroleum-ether at −5° C. the melting point rose to 117—118° C. whilst no gas was developed during melting. Repeated recrystallisation did not change the melting point any longer. In the ultraviolet region the substance (Δ^4-lumi-androstene-3), 17β-diol (Formula XVII) did not exhibit absorption.

added at 0° C., whilst adequately stirring, a solution of 0.5 mls of β-phenyl-propionyl chloride in 5 mls of dry anhydrous benzene, after which the reaction mixture was stirred at room temperature for 16 hours.

By pouring out on a mixture of 80 gs of ice and 20 mls of concentrated hydrochloric acid, the excess quantity of acidic chloride was decomposed. The ester was dissolved in benzene (three times 20 mls) and the saturated extracts were washed in succession with a sodium carbonate solution 10%) and water to neutral reaction. Drying on sodium sulphate, filtering and evaporation to dryness yielded 700 mgs of an oily product from which, after filtering in benzene through a column containing 10 gs of neutralized alumina, 590 mgs of a resin was obtained, which, after some time crystallized out. The crystalline fraction obtained by stirring with petroleum ether yielded after two recrystallisations with methanol, at −5° C., 197 mgs of β-phenyl-propionate of lumitestosterone. (Formula XIX). Melting point 73—74° C. Recrystallisation did not change the melting point.

$$E^{1\%}_{1\ cm}(\lambda_{max}\ 242\ m\mu)=421,\ 17.700$$

Calculated for $C_{28}H_{26}O_3$(420.6): C 79.97% H 8.63%
Found: C 80.00% H 8.58%
C 79.52% H 8.38%

The infrared spectrum exhibited inter alia bands at 1726 cm^{-1} (strong) 1664 cm^{-1} (strong), 1610 cm^{-1} (moderately strong) and 1173 cm^{-1}.

EXAMPLE 7

In the manner described in Example 6 other acylates are produced. For example, lumitestosterone-17-formate, lumitestosterone-17-acetate, lumitestosterone-17-propionate, lumitestosterone-17-butyrate, lumitestosterone-17-α-methylpropionate, lumitestosterone-17-valerate, lumitestosterone-17-α - methyl-butyrate, lumitestosterone-17-β-methyl - butyrate, lumitestosterone-17 - caproate, lumitestosterone-17-tert.-butylacetate, lumitestosterone - 17-trimethylacetate, lumitestosterone - 17-cyclopentyl - carboxylate, lumitestosterone - 17-cyclohexylacetate, lumitestosterone - 17 - cyclohexylcarboxylate, lumitestosterone - 17-*o*-toluate, lumitestosterone - 17-monoglutarate, lumitestosterone-17-monodiglycolate lumitestosterone - 17 - mono-β-methylglutarate, lumitestosterone-17-hemi-succinate, lumitestosterone-17-hemi-adipate, lumitestosterone - 17-acrylate, lumitestosterone-17-crotonate, lumitestosterone-17-undecylenate, lumitestosterone-17-hemi-maleate, lumitestosterone - 17-citraconate, lumitestosterone - 17 benzoate, lumitestosterone-17-phenylacetate, lumitestosterone - 17 - α - phenylpropionate, lumitestosterone-17-(*o*, *m*, *p*.)toluate, lumitestosterone-17-palmitate, lumitestosterone - 17 - stearate, lumitestosterone-17-oleate, were obtained by causing the lumitestosterone to react with the corresponding acid chloride of the aforesaid compounds in the presence of pyridine or collidine as acid binders and an indifferent solvent, for example, benzene or petroleum ether. The reaction temperature was chosen to be between 0 and 100° C., preferably between 15 and 35° C. At a reaction temperature of 70° C. to 100° C. the reaction duration amounts to 2 hours to 30 minutes. At a reaction temperature of 15 to 35° C. the reaction duration amounts from 25 to 10 hours.

EXAMPLE 8

A solution of 5 gs of lumitestosterone (Formula XVIII) was refluxed in 330 mls of freshly distilled, tertiary butanol in a nitrogen atmosphere, whilst stirring, with 8.5 gs of chloranil for 5 hours. After cooling the reaction mixture was diluted with 2 litres of water and extracted with 3×200 mls of methylene chloride. The extract, after dilution with 750 mls of petroleum ether (40 to 60° C.) was washed with 100 mls of 5% Na_2SO_4 solution with 4×50 mls of 1N NaOH and water to neutral reaction. After drying on Na_2SO_4, filtering with a small quantity of aluminium silicate and evaporation to dryness, 2.3 gs of a brown crystalline residue was obtained, which, in benzene, was filtered through 25 gs of alumina (Brockmann method II). Elution with 300 mls of benzene yielded 2.0 gs of crystalline substance

$E^{1\%}_{1\ cm}$ ($\lambda_{284m\mu}$=815).

Recrystallisation thereof with acetone-hexane at −5° C., yielded 1.43 gs, melting point 170 to 172° C. Recrystallisation yielded 1.05 gs of Δ^4-dehydro-lumitestosterone (Formula XX), melting point 173—174.5° C. From the filtrate another 240 mgs with a melting point of 167—170° C. was obtained.

For the production of the analytically pure substance recrystallisation with diethyl ether was finally carried out.

Melting point 174—175° C.

$$E^{1\%}_{1\ cm}(\lambda_{max}\ 284\ m\mu)=903,\ 893\ E_{284m\mu}=25.700$$

Calculated for $C_{19}H_{26}O_2$ (286.4): C 79.68% H 9.15%
Found: C 79.86% H 9.27%
C 79.58% H 9.09%

In the infrared spectrum are found characteristic bands at 3441 cm^{-1} (strong) OH-frequency, 1641 cm^{-1} (strong, conjugated keto-group) 1615 cm^{-1} (strong, double-bond) and 1571 cm^{-1} (weak, double bond).

EXAMPLE 9

A solution of 360 mgs of Δ^4-dehydro-lumitestosterone, obtained as described in Example 8, in 8 mls of dry, freshly distilled pyridine, was added, at 0° C., to a solution of 0.14 mls of distilled propionyl chloride in 4 mls of dry thiophene-free benzene. After stirring for 20 hours at room temperature the substance was poured out on a mixture of 50 gs of ice and 16 mls of concentrated sulphuric acid. The ester solution, obtained by extraction with benzene (three times 15 mls) was washed successively with a sodium carbonate solution (10%) and water to neutral reaction. Drying, filtering, and evaporation to dryness yielded 435 gs of residue which was crystallized with methanol at −5° C. Recrystallisation with the same solvent yielded 233 mgs of propionate of Δ^4-dehydrolumitestosterone (Formula XXI) with a melting point of 113 (light sintering) −115—117° C. Recrystallisation of a portion thereof for analysis raised the melting point to 114—115—117° C.

$$E^{1\%}_{1\ cm}(\lambda_{max}\ 286\ m\mu)=739\quad E=25{,}400$$

Calculated for $C_{22}H_{32}O_3$ (344.5): C 77.14% H 8.83%
Found: C 77.27% H 8.82%
C 77.27% H 8.68%

The infrared spectrum exhibited bands, inter alia, at 1731 cm^{-1} (strong), 1650 cm^{-1} (strong), 1618 cm^{-1} (strong) and 1571 cm^{-1} (rather strong).

EXAMPLE 10

Other acylates are produced in the manner described in Example 9. For example were obtained Δ^4-dehydrolumitestosterone-17-formate, Δ^4 - dehydrolumitestosterone-17-acetate, Δ^4 - dehydrolumitestosterone - 17 - propionate, Δ^4 - dehydro-lumitestosterone - 17 - butyrate, Δ^4 - dehydrolumitestosterone-17-α-methylpropionate, Δ^4 - dehydrolumitestosterone - 17-valerate, Δ^4 - dehydrolumitestosterone-17-α-methylbutyrate, Δ^4 - dehydrolumitestosterone-17β - methylbutyrate, Δ^4-dehydro-lumitestosterone - 17 - caproate, Δ^4 - dehydrolumitestosterone - 17 - *tert.* butylacetate, Δ^4 - dehydrolumitestosterone - 17 - trimethylacetate, Δ^4-dehydrolumitestosterone - 17 - cyclopentylcarboxylate, Δ^4 - dehydrolumitestosterone-17-cyclohexylacetate, Δ^4 - dehydrolumitestosterone-17-cyclohexylcarboxylate, Δ^4 - dehydrolumitestosterone - 17 - *o*.toluate, Δ^4-dehydrolumitestosterone - 17 - monoglutarate, Δ^4-dehydrolumitestosterone-17-monodiglycolate, Δ^4-dehydro - lumitestosterone - 17 - mono-β-methylglutarate, Δ^4 - dehydrolumitestosterone--17-hemisuccinate, Δ^4-dehydrolumitestosterone - 17 - hemiadipate, Δ^4-dehydrolumitestosterone - 17 - acrylate, Δ^4-dehydrolumitestosterone - 17 crotonate, Δ^4-dehydrolumitestosterone - 17 - undecylenate, Δ^4-dehydrolumitestosterone - 17 - hemimaleate, Δ^4-dehydrolumitestosterone - 17 - citraconate, Δ^4-dehydrolumitestosterone - 17 - benzoate, Δ^4-dehydrolumitestosterone - 17 - phenylacetate, Δ^4-dehydrolumitestosterone - 17β - phenylpropionate, Δ^4 - dehydrolumitestosterone - 17-(*o*, *m*, *p*,)toluate, Δ^4 - dehydrolumitestosterone - 17 - palmitate, Δ^4-dehydro-lumitestosterone - 17 stearate, Δ^4-dehydrolumitestosterone-17-oleate, by causing the Δ^4-dehydrolumitestosterone to react with the corresponding acid chloride of the aforesaid compounds in the presence of pyridine or colidine as an acid binder and an indifferent solvent, for example, benzene or petroleum ether. The reaction temperature is held between 0 and 100° C., preferably between 15 and 35° C. At a reaction temperature between 70 and 100° C. the reaction duration amounts from 2 hours to 30 minutes, at a reaction temperature between 15 and 35° C., the reaction duration amounts from 25 to 10 hours.

EXAMPLE 11

In a three-neck round-bottom flask of 250 mls of contents, at −80° C., 50 mls of ammonia was condensed. The ammonia gas had previously been dried by passing it through three drying towers containing solid KOH, NaOH and KOH respectively. In the condensate was then dissolved 1.61 gs of potassium, after which in the deep-blue solution acetylene gas was introduced, until a complete decolouring had taken place. This gas had been dried by means of solid KOH, soda lime, KOH, concentrated H_2SO_4 and solid KOH respectively and purified.

To the acetylide was then rapidly added, whilst stirring and cooling, at −80° C., 1.06 mls of dry acetone, after which a solution of 3.03 gs of Δ^4-lumiandrostene 3.17-dione (Formula XVI) in a mixture of 25 mls of dry thiophene-free benzene and 25 mls of dry peroxide-free diethylether was immediately added.

Whilst passing over a slow, dry nitrogen flow the reaction mixture remained without cooling from without, for 16 hours, after which it was decomposed with 175 mls of water. The clear benzene layer thus separated out was processed by washing it with water, drying on Na_2SO_4, filtering and evaporating to dryness. The 3.25 gs of residue ($E^{1\%}_{1\ cm}$ (λ_{max} 242 mμ)=288) was chromatographied

in benzene on 50 gs of Al_2O_3 (strength according to Brockmann II).

Elution with benzene (800 mls) and diethylether (200 mls) yielded crystalline fractions, which were joined and recrystallized with *n*-hexane, after which 1.95 gs of needles of 17α-ethynyl-lumitestosterone (Formula XXII) with a melting point of 194—196° C. was obtained. A small portion was recrystallized for analysis several times with *n*-hexane, after which the constant melting point was 195—196° C.

$$[\alpha]_D^{20} = -219 \ (CHCl_3) \ E\,\frac{1\%}{1\ cm}\,(\lambda_{max}\ 242\ m\mu) = 524.$$

Found: C 80.88% H 8.98%
C 80.83% H 9.11%
Calculated for $C_{21}H_{28}O_2$ C 80.73% H 9.03%

The infrared spectrum of the substance exhibited inter alia more or less strong bands at 877, 1063, 1128, 1222, 1604 and 1638 cm^{-1}.

EXAMPLE 12

To a solution of 0.5 g. of lumitestosterone, obtained as described in Example 5, in 50 mls. of dry diethylether and 75 mls. of dry, liquid ammonia, was added at the boiling temperature of the mixture, whilst adequately stirring under the exclusion of moist, drops of a solution of 500 mgs. of lithium and 75 mls. of liquid ammonia. The dark-blue-solution was then decomposed by dripping in 15 mls. of anhydrous ethanol in 30 minutes. After stirring for another half hour, the mixture was diluted with water, the ether layer was separated off and washed to neutral reaction. The resin obtained by drying the ether extract on sodium sulphate, by filtering it and evaporating it to dryness, could not be caused to crystallize. Since also chromatography *via* alumina did not cause crystallisation, the joined fractions, subsequent to evaporation to dryness, were dissolved in 5 mls. of dry thiophene-free benzene and 1 ml. of dry pyridine and then esterified by adding a solution of 650 mgs. of 3.5-dinitrobenzoyl chloride in 5 mls. of benzene.

After half an hour at room temperature the solution was decomposed by shaking it for 10 minutes with a small quantity of water, after which the ester fraction was dissolved in diethyl ether. The extract obtained was then washed with water, 2N hydrochloric acid, water, sodium bicarbonate solution and water. Drying on sodium sulphate, filtering and evaporating to dryness yielded 600 mgs of a light-yellow resin, which could be cause to crystallize from a mixture of methylene chloride and acetone. The final yield was 270 mgs of bis - (3, 5 dinitrobenzoate) of 5 - lumiandrostene - 3, 17β - diol (Formula XXIII) with a melting point of 237—242° C.

Calculated for $C_{33}H_{36}O_{12}N_4$ (680.65) C 58.23% H 5.33% N 8.23%
Found: C 58.34% H 5.49% N 7.85%
C 58.31% H 5.68% N 7.88%

EXAMPLE 13

To a solution of 1 g of lumitestosterone, produced as described in Example 5, in 35 mls of benzene was added 1 g of selenium dioxide and 0.6 ml of water, after which the mixture was refluxed in a nitrogen atmosphere for 48 hours.

After filtering and washing the solid constituents with benzene the filtrate was washed successively with a bicarbonate solution and water. The dried and filtered solution was evaporated to dryness in vacuo, after which 625 mgs of a resin was obtained with

$$E\,\frac{1\%}{1\ cm}\,(\lambda_{max}\ 243\ m\mu) = 358.$$

By a further extraction of the solid constituents, after the reaction (selenium diode and so on) with carbon tetra chloride and working up another 50 mgs of resin was obtained. The total quantity was then dissolved in benzene and chromatographed on 40 gs of alumina.

Fraction	Eluate	Volume	Weight
1.	benzene	150 ml	<10 mg
2.	benzene+ether 2:1	200 ml	20 mg
3.	ditto 1:2	300 ml	190 mg partly crystalline
4.	ditto 1:2	250 ml	50 mg partly crystalline
	ether	300 ml	
5.	acetone	100 ml	240 mg partly crystalline

Fractions 3 and 4 were crystallized with *n*-hexane (twice), after which 150 mgs of substance with a melting point of 164 (slight sintering)—172—173° C. was obtained.

Recrystallisation with a mixture of *n*-hexane and methylene chloride yielded 98 mgs of Δ^1 - dehydrolumitestosterone (Formula XXIV) melting point 171—175—177° C.

$E^{1\%}_{1\ cm}$ (λ_{max} 243.5 mμ)=538. E=15.300.

Calculated for $C_{19}H_{26}O_2$ (286.4): C 79.68% H 9.15%
Found: C 79.44% H 9.07%
C 79.07% H 9.15%

The infrared spectrum exhibited inter alia bands at 3364 cm^{-1} (strong), 1650 cm^{-1} (strong), 1609 cm^{-1} (fairly strong), 1592 cm^{-1} (weak) and 884 cm^{-1}.

EXAMPLE 14a

To a solution of 1.14 gs of lumitestosterone, produced as described in Example 5, in 10 mls of dry thiophene-free benzene was added, under nitrogen, in order of succession: 0.6 ml of diethyl oxalate, and 200 mgs of sodium hydride. Then the reaction mixture was stirred under nitrogen for 72 hours at room temperature, the colour passing then over from brown to yellow and a voluminous deposit being formed.

After the addition of 5 mls of methanol water was used for dilution, the solution was extracted with diethylether to remove substance non-soluble in water. The aqueous layer was acidified with 2N hydrochloric acid and the separated substance was dissolved in diethylether. The extract was then washed to be free of hydrochloric acid with a saturated sodium chloride solution, dried on sodium sulphate, filtered and evaporated to dryness, after which a light-yellow resin of the enol of 2 - (ethoxyoxalyl) lumitestosterone (Formula XXV) was obtained.

EXAMPLE 14b

A solution of 1.3 gs of a compound of the Formula XXV in 25 mls of dry, purified acetone was refluxed with 2 mls of methyl iodide for 18 hours in the presence of 1 g of dry potassium carbonate. After cooling the solution was diluted with water and dissolved in diethyl ether, after which the extract was washed with 1N caustic soda lye and water to neutral reaction, dried on sodium sulphate and, after filtering evaporated to dryness.

The 1.05 gs of residue was boiled with a solution obtained by reacting 0.5 g of sodium in 10 mls of anhydrous ethanol. After cooling the mixture was poured out in water and the separated substance was dissolved in diethyl ether, washed with water, dried on sodium sulphate, filtered and evaporated to dryness, after which 0.515 g of resinous substance was obtained, which could not be caused to crystallize without the need for further measures. Chromatography *via* 25 gs of alumina in benzene yielded the following fractions:—

Fraction	Eluate	Volume	Weight
1.	benzene	50 mls	12 mgs
2.	benzene	100 mls	150 mgs
3.	benzene	100 mls	111 mgs
4.	benzene	250 mls	112 mgs

Two recrystallisations with a mixture of diethyl ether and *n*-hexane of the fractions 2 to 4 yielded 207 mgs of 2 - methyl - lumitesto - sterone (Formula XXVI) with a melting point of 175—179° C. For analysis a portion was recrystallized again, after which the melting point was 177—179.5° C.

$E^{1\%}_{1\ cm}$ (λ_{max}=241.5 mμ)=508. E=15,400.

Calculated for $C_{20}H_{30}O_2$ (302.46): C 79.41% H 10.00%
Found: C 79.50% H 9.98%
C 79.81% H 9.84%

EXAMPLE 15a

A solution of 7.5 gs of lumiprogesterone (Formula VIII) in 500 mls of freshly distilled tertiary butyl alcohol was refluxed with 12.75 gs of finely powdered chloranil whilst stirring for 5 hours under nitrogen. After cooling 2 litres of water was added and extraction was performed three times with 200 mls of methylene chloride. The extracts were then bulked, diluted with 1 litre of petroleum ether (40—60° C.) and washed successively with diluted Na_2SO_4, (100 mls), 4×75 mls of 1N NaOH and water to neutral reaction.

By drying on Na_2SO_4 and evaporating to dryness (last part in vacuo) 3.7 gs of crystalline residue was obtained.

Filtration thereof in benzene via 35 gs of alumina (according to Brockmann strength II) and eluation with benzene, and after evaporation of the solvent yielded 3.11 gs of crystalline residue. By crystallisation with 15 mls of acetone at room temperature (at lower temperatures a by-product crystallized out) this yielded 900 mgs of crystallate with a melting point of 165—170° C. Transfer of the mother liquor into a mixture of ethanol and hexane yielded 1.7 gs of substance with a melting point of 130 to 145° C. This fraction of hexane was then recrystallised with acetone (room temperature), after which 600 mgs with a melting point of 166 to 171° C. was obtained. The two fairly pure fractions yielded, after crystallisation with a mixture of acetone and hexane, finally 1.0 g of Δ^6 - dehydro -

lumiprogesterone (Formula XXVII), melting point 169 to 170° C. From the mother liquors a further fraction of 0.44 g with a melting point of 168 to 169° C. was obtained.

A small portion was again recrystallized with acetone for analysis; the melting point rose to 169—170° C.

$E^{1\%}_{1\ cm}$ (λ_{max}=286.5 mμ)=842 and 848 E=286.5 mμ=26,400.

Calculated for $C_{21}H_{28}O_2$ (312.43): C 80.73% H 9.03%
Found: C 81.11% H 9.20%
C 81.25% H 9.07%

The infrared spectrum exhibited inter alia bands at 1695 cm^{-1} (strong, non conjugated keto group), 1656 cm^{-1} (strong, conjugated keto group), 1617 cm^{-1} (strong, double bond in conjugation), 1574 cm^{-1} (moderately strong, double bond) and 888 cm^{-1} (strong).

EXAMPLE 15b

3.95 gs of isolumisterone obtained as described in Example 1a (Formula II) was dissolved in 150 mls of dry methylene chloride. To this solution was added 0.81 ml of dry pyridine. The solution thus obtained was cooled to −80° C. and then, within 26 minutes, 14 mmol of ozone (i.e. 140% of the theoretical volume) was passed through. The reaction mixture was then vigorously stirred, after which 15 gs of paraformaldehyde was added. Under constant stirring the temperature rose within 4 hours to about room temperature. After one night the solid substance was filtered off, washed with petroleum-ether and ether. The solution was then washed with water, cold N NaOH and water. After drying on Na_2SO_4 the solution was evaporated 3.08 gs of residue was obtained. $E^{1\%}_{1\ cm}$ (λ_{max} 286 mμ)=770 (self-registering). This residue was crystallized with acetone and then recrystallized twice.

The pure 3 - keto - lumi - bis - nor - chola - 4.6 - diene - 22 - al (Formula XXVIII) has a melting point of 153—155° C. The ultraviolet absorption spectrum has a maximum at 286 mμ. $E^{1\%}_{1\ cm}$=780 E=25,400.

Calculated for $C_{22}H_{30}O_2$=326.48: C 80.94% H 9.26% O 9.80%
Found: C 81.07% H 9.16% O 9.94%
C 80.87% H 9.05% O 10.00%

The following bands in the infrared spectrum were found: 1410 cm^{-1} (weak), 1654 cm^{-1} (strong), 1717 cm^{-1} (strong), 1584 cm^{-1} (strong), 1621 cm^{-1} (fairly strong).

EXAMPLE 15c

3.5 gs of the aldehyde obtained as described in Example 15b, (crude crystalline, melting point 146—151° C.) was dissolved in 50 mls of absolute benzene; there was added 1.27 mls of piperidine and 20 mgs of *p*-toluenesulphonic acid. This reaction mixture was refluxed for two and a half hours, the refluxing solvent being dried through BaO. Then the solvent was distilled off in vacuo. 4.4 gs of residue was left (150%). This was crystallized with 30 mls of methanol at −25° C. Yield: 2.1 gs of 22 - (N - piperidino) - lumi - bis - nor - chola - 4, 6, 20 (22) - triene - 3 - one (Formula XXIX) with a melting point of 127—135° C. After two recrystallisations with acetone the substance was pure.

Melting point (in vacuo) 135—136° C.

Ultraviolet absorption spectrum had a maximum at 287 mμ.

$E^{1\%}_{1\ cm}$=661 and 657. E=26,000 and 25,800.

Calculated for $C_{27}H_{39}NO$: 393.62: C 82.39% H 9.99% O 4.06% N 3.56%
Found: C 82.40% H 9.86% O 4.35% N 4.13%

There were found bands in the infrared spectrum at 870 cm^{-1} (strong), 1656 cm^{-1} (strong), 1622 cm^{-1} (strong), 1410 cm^{-1} (weak).

EXAMPLE 15d

16.7 gs of the crude enamine thus obtained in Example 15c dissolved in 250 mls of dry thiophene-free benzene, was added in dropwise during 45 minutes, to an adequately stirred solution of 25.2 gs of sodium bichromate in 250 mls of acetic acid + 170 mls of benzene, cooled to 0° C. After two hours of stirring at 0° C., 42.0 mls of methanol was added and stirring was continued for half an hour at 0° C. The reaction mixture was then poured out in water and extracted with ether. The extract was washed with water dilute sodium hydroxide solution and water. After drying on Na_2SO_4 the solvent was distilled off. Yield: 12.24 gs (92%) of residue. This was crystallized with acetone-hexane (6.6 gs) and then by two crystallisations with acetone the substance obtained was pure. The melting point of the Δ^6-dehydrolumiprogesterone thus obtained (Formula XXVII) was 168—169° C.

EXAMPLE 15e

3.95 gs of lumisterone (Formula I) was dissolved in 150 mls of dry methylene chloride and to this solution was added 0.81 ml of

pyridine. At −70° C., within 26 minutes, 14 mmol of ozone was passed through. Then 15 gs of para-formaldehyde was added and whilst stirring the temperature was slowly increased to +5° C. The para-formaldehyde was filtered off and washed with methylene chloride. The filtrate was washed with water 1 N NaOH solution and water. After drying on Na_2SO_4 the solvent was distilled off, after which 3.11 gs of crystalline residue was left. It was recrystallized with a mixture of methylene chloride and acetone. After three recrystallisations pure 3 - keto - lumi - bis - *nor* - chola - 4, 7 diene - 22 - al was obtained (Formula XXX) with a melting point of 196—200° C. The ultraviolet absorption spectrum had a maximum at 241 mμ.

$E\,^{1\%}_{1\ cm}$ 433 and 436—E 14,150 and 14,200.

Calculated for $C_{22}H_{30}O_2$ 326.48: C 80.94% H 9.26% 9.80%
Found: C 80.15% H 9.13% O 10.10%
C 80.28% H 9.09% O 10.04%

The infrared absorption spectrum has bands, inter alia, at 1410 cm^{-1} (weak) 1660 cm^{-1} (strong), 1610 cm^{-1} (strong) and 1714 cm^{-1} (strong).

When the aldehyde thus obtained was converted in the manner described in Example 1e or 15 into the enamine, which compound was oxidized with sodium bichromate in benzene and acetic acid in the manner described in Example 1g, or 15d, the Δ^7 - dehydrolumi - progesterone (Formula XXXI) was obtained. By isomerisation of the 3 - keto - $\Delta^{1,7}$ - system of compounds of the Formula XXXI into the 3 - keto - $\Delta^{4,6}$ - system with dry HCl-gas in anhydrous isopropanol, in the manner described in Example 1a, the Δ^6 - dehydrolumi - progesterone (Formula XXVII) is obtained.

Example 16

To a solution of 0.978 g (3 mmol) of the aldehyde obtained as described in Example 3a or 3c (Formula XIV) ("unsaturated side chain aldehyde") in 10 mls of dry thiophene-free benzene was added whilst cooling with ice water, a solution of 1.2 gs of monoperphthalic acid (6.6 mmol) in 25.5 mls of ethyl acetate of 0° C.

Of the remaining quantity of reaction mixture the phthalic acid formed was filtered off and the filtrate obtained was washed successively with a 10% solution of sodium bicarbonate and water, dried on Na_2SO_4 and after filtering evaporated to dryness. 0.88 g of a substantially colourless resin was obtained, which could not be caused to crystallize.

The hydrolysis of the 17 (20) - epoxy - formate (Formula XXXII) was carried out by providing a solution of the substance in 150 mls of ethanol (95%) at 30° C. with 35 mls of aqueous 3.0N sodium hydroxide solution at room temperature, the reaction mixture assuming a clear yellow colour. After two hours, without cooling or heating, at room temperature, neutralisation at 6 mls of acetic acid was carried out. The light-yellow solution thus obtained was concentrated at the lowest possible temperature in water-jet pump vacuum, to about 60 mls, after which 100 mls of water was added. The oil separated out was dissolved in two extractions in ether and the solution, after having been washed with a diluted bicarbonate solution and water and drying on Na_2SO_4 filtered. By evaporating to dryness 580 mgs of crystalline residue was obtained, $E\,^{1\%}_{1\ cm}$ (λ_{max} 242.5 mμ)=504. After three recrystallisations with ethanol at −5° C. 118 mgs of hard crystals of 17 (α) - hydroxy - lumiprogesterone (Formula XXXIII) was obtained with a melting point of 222—225° C.

$E\,^{1\%}_{1\ cm}$ (λ_{max} 242 mμ)=500. E 242 mμ=15,500.

Calculated for $C_{21}H_{30}O_3$ (330.45): C 76.32% H 9.15%
Found: C 76.07% H 9.14%
C 75.84% H 9.10%

The infrared spectrum exhibited bands inter alia at 3369 cm^{-1} (strong, hydroxyl band), 1697 cm^{-1} (strong, unconjugated keto group), 1643 cm^{-1} (strong, conjugated keto-group), 1610 cm^{-1} (fairly strong, double bond) 1354 cm^{-1}, 1232 cm^{-1}, 928 cm^{-1}, 858 cm^{-1}.

Example 17

A solution of 220 mgs of 17α - hydroxy - lumiprogesterone, produced as described in Example 16, and 220 mgs of *p*-toluenesulphonic acid in 15 mls of distilled acetic anhydride was kept at room temperature for 18 hours. A small number of fine needles of a very dark reaction mixture crystallized out. By pouring out in ice water and after the addition of a small quantity of pyridine, and stirring for some time, the excess acetic anhydride was decomposed and the ester was extracted in ether (three times 30 mls) and methylene chloride (one 30 mls). The collected extracts were then washed successively with water, 2N sulphuric acid (to pyridine free) water, 5% bicarbonate solution and water, dried on sodium sulphate and after filtering evaporated to dryness, a complete crystalline residue being obtained. Crystallisation with a mixture of methylenechloride and methanol at

—5° C. yielded 130 mgs of crystals of the diacetate of 3, 17α - dihydroxy - 20 - keto - $\Delta^{4,5}$ - lumipregnadiene (Formula XXXIV), melting point 207—(sintering)—213—216° C. Two recrystallisations with the same mixture yielded a constant melting point of 207—(sintering—213—216° C. In high vacuo the melting point was 217—218° C.

$E\ {}^{1\%}_{1\ cm}$ (λ_{max}=236.5 mμ)=445 and 439. E=236.5 mμ=18,300.

Calculated for $C_{25}H_{34}O_5$: C 72.43% H 8.27%
Found: C 71.71% H 8.21%
C 71.78% H 8.12%

The infrared spectrum exhibited bands, inter alia at 1744 cm^{-1} (broad and strong, acetate group (twice)), 1707 cm^{-1} (strong, unconjugated keto group), 1661 cm^{-1} (weak), 1624 cm^{-1} (very weak) 1248 cm^{-1} (strong) and 900 cm^{-1} (strong).

EXAMPLE 18

A solution of 500 mgs of 17α - hydroxy - lumiprogesterone, produced as described in Example 16, and 500 mgs of *p*-toluenesulphonic acid in a mixture of 5 mls of freshly distilled acetic anhydride and 25 mls of acetic acid was kept at room temperature for 15 hours. The acetic acid had previously been made free of water by refluxing with acetic anhydride, followed by fractionating.

The dark-coloured reaction mixture was poured out in 200 mls of water and the reaction product was dissolved in methylene chloride. The extract was, after the addition of ether, washed successively with water, 5% bicarbonate solution (three times) and water. By drying on sodium sulphate and evaporating to dryness a crystalline residue was obtained, which was dissolved in ethanol. Injection of diacetate obtained as described in Example 17 caused a small quantity of this ester to crystallize at room temperature. Filtering after three hours yielded 75 mgs of diacetate with a melting point of 205—(sintering)—211° C.—214° C. The filtrate was slightly concentrated and crystallized at −5° C. Yield 260 mgs of 17(α) acetoxy - lumiprogresterone (Formula XXXV) with a melting point of 162 (sintering) —167—172° C. Two further recrystallisations caused the melting point to be constant at 169 (sintering—171—173° C.

$E\ {}^{1\%}_{1\ cm}$ (λ_{max} 241.5 mμ)=444 and 452. E 241.5 mμ=16,700.

Calculated for $C_{23}H_{32}O_4$: C 74.16% H 8.66%
Found: C 73.81% H 8.69%
C 73.88% H 8.68%.

The infrared spectrum exhibited bands inter alia at 1724 cm^{-1} (strong, acetate keto-group), 1707 cm^{-1} (fairly strong, unconjugated keto-group), 1657 cm^{-1} (strong conjugated keto-group), 1611 cm^{-1} (fairly strong double bond), 1256 cm^{-1} and 871 cm^{-1}.

EXAMPLE 19

900 mgs of 17α - hydroxy - lumipro - gesterone, obtained as described in Example 16 was shaken for 15 hours in 20 mls of caproic anhydride under nitrogen with 1.1 gs of *p*-toluene sulphonic acid. The dark-coloured reaction mixture was then, after the addition of 20 mls of ethanol and 0.3 ml of concentrated hydrochloric acid, refluxed for one hour, after which 30 mls of pyridine was added. Then *in vacuo*, evaporation to dryness was carried out and the residue was dissolved in methylene chloride. The solution obtained, after having been washed with water was dried to neutral reaction on Na_2SO_4 and finally evaporated to dryness, after which 1.25 gs of a resinuous product was obtained. The substance could not be caused to crystallize, even after filtering in benzene *via* 18 gs of neutral alumina. The neutral alumina was produced by suspending the commercial product for 6 hours in boiling ethyl acetate and after filtering, drying at 1100° C. After elution with benzene and evaporation of the eluate 1.1 gs of resin with $E\ {}^{1\%}_{1\ cm}$ (λ_{max} 241 mμ)=310 was obtained.

The residue was chromatographed, after careful drying (for two hours at 60° C. at a pressure of 0.1 mm Hg) in petroleum-ether, which contained 5% of diethyl ether via 25 gs of neutral alumina and eluated with the same mixture.

No.	Eluate	Weight	Crystallisation with *n*-hexane
1	50 ml	68 mg	
2	30 ml	438 mg	354 mg, melted after filtering
3	30 ml	117 mg	83 mg, smpt (50)—51—54° C.
4	30 ml	121 mg	61 mg, smpt. 44—52° C.
5	30 ml	27 mg	crystalline
6	30 ml	16 mg	„
7	50 ml	11 mg	„
8	50 ml	6 mg	„

The crystallized fractions 3 and 4 exhibited, after two recrystallisations a melting point of 50—53° C. (weight 67 mgs). The 17-caproate of 17α - hydroxylumiprogesterone (Formula XXXVI) exhibited an $E^{1\%}_{1\ cm}$ (λ_{max} 242 mμ) of 388).

Calculated for $C_{27}H_{42}O_4$: C 75.66% H 9.41%
Found: C 75.15% H 9.22%,
C 75.40% H 9.30%.

The infrared spectrum had bands, inter alia, at 1721 cm^{-1} (strong, keto-caproxy), 1709 cm^{-1} (strong, unconjugated keto group), 1664 cm^{-1} (strong, conjugated keto-group) and 1613 cm^{-1} (fairly strong, double bond).

EXAMPLE 20

In the manner described in Examples 18 and 19 other acylates are produced. For example are obtained: 17α - hydroxylumiprogesterone - 17α - formate, 17α - hydroxy - lumiprogesterone - 17α - acetate, 17α - hydroxylumiprogesterone - 17α - propionate, 17α - hydroxylumiprogesterone - 17α - butyrate, 17α - hydroxylumiprogesterone - 17α - α - methylpropionate, 17α - hydroxylumiprogesterone - 17α - valerate, 17α - hydroxy - lumiprogesterone - 17α - α - methylbutyrate, 17α - hydroxy - lumiprogesterone 17α - β - methylbutyrate - 17α - hydroxylumiprogesterone - 17α - caproate, 17α - hydroxy - lumiprogesterone - 17α - *tert* - butylacetate, 17α - hydroxylumiprogesterone - 17α - trimethylacetate, 17α - hydroxylumiprogesterone-17α - cyclopentylcarboxylate, 17α - hydroxy - lumiprogesterone - 17α - cyclohexylcarboxylate, 17α - hydroxylumiprogesterone - 17α - *o*-toluate, 17α - hydroxylumiprogesterone - 17α - monoglutarate, 17α - hydroxylumiprogesterone - 17α - monodiglycolate, 17α - hydroxylumiprogesterone - 17α - mono - β - methyl - glutarate, 17α - hydroxylumiprogesterone - 17α - hemisuccinate, 17α - hydroxylumiprogesterone - 17α - hemiadipate, 17α - hydroxylumiprogesterone - 17α - acrylate, 17α - hydroxylumiprogesterone - 17α - crotonate, 17α - hydroxy - lumiprogesterone - 17α - undecylenate, 17α - hydroxylumiprogesterone - 17α - hemimaleate, 17α - hydroxy - lumiprogesterone - 17α - citraconate, 17α - hydroxylumiprogesterone - 17α - benzoate, 17α - hydroxylumiprogesterone - 17α - phenylacetate, 17α - hydroxylumiprogesterone - 17α - phenylpropionate, 17α - hydroxylumiprogesterone - 17α (*o.m.p.*) - toluate, 17α - hydroxylumiprogesterone - 17α - palmitate-17α - hydroxylumiprogesterone - 17α - stearate, 17α - hydroxylumiprogesterone - 17α - oleate by causing the 17α - hydroxylumiprogesterone to react with the corresponding acid chlorides in the presence of pyridine or collidine as an acid binder and an indifferent solvent, for example, benzene or petroleum ether. The reaction temperature was kept between 0 and 100° C., preferably between 15 and 35° C. At a reaction temperature between 70 and 100° C., the reaction duration amounts between 2 hours and 30 minutes. At a reaction temperature between 15 and 35° C. the duration is from 25 to 10 hours.

EXAMPLE 21

A solution of 0.495 g of 1.5 mol 17α-hydroxylumiprogesterone, produced as described in Example 16, in 60 mls of tertiary butanol was refluxed under nitrogen with 0.74 g (3 mmol) of chloranil. After 2 and 4 hours samples were taken and processed by pouring out in water, dissolving in methylene chloride-ether and washing with 2N caustic soda solution and water. The residues obtained by drying on Na_2SO_4 and after filtering and evaporation to dryness, exhibited an absorption maximum at λ=286 mμ with an $E^{1\%}_{1\ cm}$ of 203 and 462 respectively.

After a reflux time of in total 7 hours the reaction mixture was processed as stated above and filtered in benzene *via* neutral alumina. 180 mgs of crude substance was obtained. Crystallisation with a mixture of ethanol-hexane at −5° C. yielded 97 mgs with a melting point of 229—(sintering)—239—244° C. Two recrystallisations yielded finally 50 mgs of Δ⁴ - dehydro - 17α - hydroxy-lumiprogesterone (Formula XXXVII) with a melting point of 242—245° C. (high-vacuum 243—245° C.).

$E^{1\%}_{1\ cm}$ (λ_{max} 286 mμ)=776 and 756. E 286 mμ 25.100.

Calculated for $C_{21}H_{28}O_3$ (328.45) C 76.79% H 8.59%.
Found: C 76.38% H 8.61%
C 76.64% H 8.50%.

The infrared spectrum had bands, inter alia, at 3344 cm^{-1} (strong hydroxyl group), 1667 cm^{-1} (strong, unconjugated group) 1641 cm^{-1} (strong, conjugated keto group), 1612 cm^{-1} (strong, double bond), 1576 cm^{-1} (fairly strong, double bond), 873 cm^{-1} (fairly strong, conjugated keto group).

EXAMPLE 22

A solution of 372 mgs of (1 mmol) of 17α-acetoxylumiprogesterone, obtained as des-

cribed in Example 18, was refluxed in 40 mls of tertiary butanol under nitrogen, with 490 mgs (2 mmol) of chloranil. After different reaction times samples were taken and processed as described in Example 21. Of the crude dehydrogenation products obtained the ultraviolet spectres were determined; it was found that after 11 hours of refluxing the $E\,^{1\%}_{1\,cm}$ at 286 mμ had risen to 585. Processing of the reaction mixture in total, after the said time, yielded 152 mgs of residue, which was crystallized with acetone and then recrystallized with a mixture of acetone and hexane. At −5° C., whilst finally 32 mgs of crystals of Δ^4 - dehydro - 17α - acetoxy - lumiprogesterone (Formula XXXVIII) was obtained with a melting point of 181—182° C.

$E\,^{1\%}_{1\,cm}$ (λ_{max} 286 mμ)=622 and 633 E286 mμ=23,200.

Calculated for $C_{23}H_{30}O_4$ (370.49): C 74.54% H 8.16%
Found: C 73.85% H 8.13%
C 73.75% H 8.16%

The infrared spectrum had bands, inter alia, at 1724 cm^{-1} (strong, ketoacetate group), 1704 cm^{-1} (strong, unconjugated keto group), 1653 cm^{-1} (strong, conjugated ketogroup), 1625 cm^{-1} (fairly strong, double bond), 1685 cm^{-1} (fairly weak, double bond) 1258 cm^{-1} (strong, acetate group) and 878 cm^{-1} (strong conjugated keto group).

The compound was also obtained by esterifying Δ^6 - dehydro - 17α - hydroxylumiprogesterone with acetic anhydride in the manner described in Example 18.

EXAMPLE 23

In the manner described in Example 22 other acelates are produced. For example, Δ^6 - dehydrolumiprogesterone - 17α - formate, Δ^6 - dehydrolumiprogesterone - 17α - acetate, Δ^6 - dehydrolumiprogesterone - 17α - propionate (Δ^6 - dehydrolumiprogesterone - 17α - butyrate) Δ^6 - dehydrolumiprogesterone - 17α - α - methylpropionate, Δ^6 - dehydrolumiprogesterone - 17α - valerate, Δ^6 - dehydrolumiprogesterone - 17α - α - ethylbutyrate, Δ^6 - dehydrolumiprogesterone - 17α - β - methylbutyrate, Δ^6 - dehydrolumiprogesterone 17α - caproate, Δ^6 - dehydrolumiprogesterone - 17α - *tert* - butylacetate, Δ^6 - dehydrolumiprogesterone - 17α - trimethylacetate, Δ^6 - dehydrolumiprogesterone - 17α - cyclopentyl - carboxylate, Δ^6 - dehydrolumiprogesterone - 17α - cyclohexylacetate, Δ^6 - dehydrolumiprogesterone - 17α - cyclohexylcarboxylate, Δ^6 - dehydrolumiprogesterone - 17α - o - toluate, Δ^6 - dehydrolumiprogesterone - 17α - monoglutarate, Δ^6 - dehydrolumiprogesterone - 17α - monodiglycolate, Δ^6 - dehydrolumiprogesterone - 17α - mono - β - methylglutarate, Δ^6 - dehydrolumiprogesterone - 17α - hemisaccanate, Δ^6 - dehydrolumiprogesterone - 17α - hemiadipate, Δ^6 - dehydrolumiprogesterone - 17α - acrylate, Δ^6 - dehydrolumiprogesterone - 17α - crotonate, Δ^6 - dehydrolumiprogesterone - 17α - andecylenate, Δ^6 - dehydrolumiprogesterone - 17α - hemimaleate, Δ^6 - dehydrolumiprogesterone - 17 - α - citraconate, Δ^6 - dehydroluminprogesterone - 17α - benzoate, Δ^6 - dehydrolumiprogesterone - 17α - phenylacetate, Δ^6 - dehydrolumiprogesterone - 17α - phenylpropionate, Δ^6 - dehydrolumiprogesterone - 17α - (*o*, *m*, *p*) toluate, Δ^6 - dehydrolumiprogesterone - 17α - palmitate Δ^6 - dehydrolumiprogesterone - 17α - stearate, Δ^6 - dehydrolumiprogesterone - 17α - oleate, by causing the Δ^6 - dehydro - 17α - hydroxy - lumiprogesterone to react with the corresponding acid chloride of the aforesaid compounds in the presence of pyridine or collidine as an acid binder and an indifferent solvent, for example benzene or petroleum ether. The reaction temperature is kept between 0 and 100° C., preferably between 15° and 35° C.

EXAMPLE 24

6.5 gs of enamine, obtained as described in Example 15c, (Formula XXIX) was dissolved in 321 mls of methylene chloride whilst stirring, at a temperature of −55° C. a solution of 2.77 gs of bromine in 34 mls of methylene chloride was dripped in. The temperature was then brought to about 0° C., after which the reaction mixture was hydrogenated by vigorously stirring for 2 hours with 40.5 mls of water. The methylene chloride solution was then separated off, washed twice with 110 mls of water and dried on Na_2SO_4. A solution of 20 - bromo - 3 - keto - lumi -*bis* - *nor* - chola - 4.6 - diene - 22 - al (Formula XXXIX) was obtained.

To the solution of 20 - bromo - 3 - keto - lumi - *bis* - *nor* - chola - 4.6 - triene - 22 - al in methylene chloride was added 13.5 mls of pyridine, after which the methylene chloride was distilled off *in vacuo*. Then 33.5 mls of pyridine was added and heated first for one hour at 70° C. and then for half an hour at 100° C. The pyridine was distilled off in vacuo and the residue was dissolved in methylene chloride. This solution was washed successively with 2N hydrochloric acid, water, sodium carbonate solution and water. After drying over Na_2SO_4 the solution was evaporated and the residue (5.06 gs) was crystallized with 25 mls of acetone. After repeated crystallisation with acetone pure 3 -

keto - lumi - *bis* - *nor* - chola - 4.6, 17 (20) - triene - 22 - al (Formula XI) was obtained. Melting point 190—196 C. Ultraviolet spectrum in ethanol: one maximum at 281 mμ,

$$E^{1\%}_{1cm}\ 1070.$$

Calculated for $C_{32}H_{32}O_2$ (524.46): C 81.44% H 8.69%
Found: C 81.63% H 8.51%
C 81.52% H 8,60%

The infrared absorption spectrum exhibited bands at 1410 cm^{-1} (weak), 1655 cm^{-1} (strong) 1616 cm^{-1} and 1574 cm^{-1} (fairly strong). When in the manner described in Example 16 the latter compound is epoxidized with monoperphthalic acid, an epoxyformate of Formula XLI is obtained. Hydrogenation of this compound in the manner described in Example 16 with ethanolic aqueous NaOH solution at room temperature yields Δ^6 - de - hydro - 17α - hydroxylumiprogesterone (Formula XXXVI). When the 3 - keto - lumi - bis - *nor* - chola - 4.6 - 17 (20) - triene - 22 - al (Formula XL) is converted into the cyanhydrin as described in Example 3b, c and the compound thus obtained is subjected to ozonisation, also as described in Examples 3b or 3c, the $\Delta^{4,6}$ - lumi - androstadiene 3,16 - dione of Formula XLII is obtained. After reduction with $LiAlH_4$, followed by oxidation with manganese dioxide in $CHCl_3$ as described in Example 4 or 5, Δ^6 - dehydro-lumitesto - sterone (Formula XX) is formed.

EXAMPLE 25.

A solution of 1 g of isolumisterone, obtained as described in Example 1a was dissolved in 50 mls of dry diethyl ether whilst adequately stirring in the course of 10 minutes, added to a solution of 100 mgs of lithium in 200 mls of liquid ammonia at the boiling temperature of the mixture. During the addition a precipitate is formed. By dripping in anhydrous alcohol, the excess quantity of lithium was decomposed and after stirring for 6 minutes the reaction mixture was diluted with water and extracted with ether. The collected extraction layers were adequately washed with water, dried on Na_2SO_4 and, after filtering, evaporated to dryness. The lightbrown residue was dissolved in a small quantity of dry thiophene-free benzene, chromatographied on Al_2O_3 (III) and eluated with 60 mls of benzene. The light-yellow resin obtained after evaporation in vacuo exhibited an ultraviolet absorption maximum at 242 mμ. $E^{1\%}_{1\ cm}$ =209. (Weight 906 mgs).

The crystallisation with 10 mls of acetone + methanol (1:1) at 25° yielded 510 mgs of solid substance with a melting point of 74—82° C. (sintering at 70° C., clear melt at 100° C.). By dissolving the substance in boiling ethyl acetate and crystallizing the solution at 20° C., a small quantity of the substance with a melting point 110—114° C. ($E^{1\%}_{1\ cm}$ 242 mμ=122) was obtained. The filtrate yielded by crystallisation at −25° C. 100 mgs of light-yellow needles with a melting point 82—84° C. Recrystallisation with acetone + methanol (1+4) at −5° C. yielded finally 80 mgs of $\Delta^{5,7}$ - lumistadiene - 3 - one (Formula XLIII) with a melting point of 88—90° C.

The substance had in the ultraviolet region no absorption. The infrared spectrum exhibited a strong band at 1720 cm^{-1} and a weaker band at 962 cm^{-1} $[\alpha]_D$ −61.3 in $CHCl_3$.

Found: C 84.28% H 10.96%
C 84.33% H 10.94%
Calculated for $C_{24}H_{34}O$: C 84.79% H 11.17%.

EXAMPLE 26

The compounds according to the invention may be processed in known manner to obtain pharmaceutic preparations, for example, tablets, dragees, or injection liquids by mixing the substances with or dissolving or dispersing then in solid or liquid diluents respectively. Suitable tablets of lumiprogesterone may be obtained, for example, by preparing a mixture of the following composition:—

lumiprogesterone - - -	1 mg
gelatin - - - - -	2.5 mg
lactose - - - - -	220 mg
talcum - - - - -	24.5 mg
magnesium stearate - -	2.0 mg
	250 mg.

The preparation of certain specific compounds has been described in the foregoing specific description, with especial reference to operations upon the side-chain at the 17-position in the steroid nucleus. It will be understood that within the scope of the invention, other starting materials may be employed, and other known process steps incorporated, to obtain other products within the scope of the appended claims, and more particularly to introduce in known manner or as described more fully above, other different substituents in various positions in the steroid nucleus, which introduction may be effected at a convenient stage in the process. For example, a Δ^1 double bond may be introduced, as described in Chapter X, by selective dehydrogenation using

halogenation followed by dehydrohalogenation: direct biochemical dehydrogenation; iodine pentoxide or iodic acid; or selenium dioxide or selenic acid. To introduce 2-substituents, reaction as described in Chapter XI may be effected, viz., with a dialkyl oxalate, followed by reaction with an alkyl halide to give a 2-alkyl substituent, or with halogen as described in Chapter IX of the same to give a 2-halo compound convertible by means of an acylating agent into a 2-ester compound which can further be saponified and etherified to give 2-OH and 2-ether compounds respectively. N-bromo-succinimide or other acid N-halo-amide or -imide may be employed to effect allylic substitution yielding a 6-halo compound.

WHAT WE CLAIM IS:—

1. A compound having the general formula A shown in the accompanying drawings wherein:—

R_1 represents hydrogen or a methyl group,

R_2 represents no double bonds or one or more double bonds at one or more of positions 1, 2, 3, 4, 5, 6, 15 and 16,

R_3 represents hydrogen, a methyl or ethyl group, or a hydroxy or etherified or esterified hydroxy group,

R_4 represents a keto group or a hydroxy group or an etherified or esterified hydroxy group,

R_5 represents hydrogen or a halogen atom,

R_6 represents hydrogen, a halogen atom, a methyl group, or a hydroxy or etherified or esterified hydroxy group,

R_7 represents hydrogen or a halogen atom,

R_8 represents hydrogen or a hydroxy or keto group,

R_9 represents hydrogen or a saturated or unsaturated hydrocarbon radical having from one to six carbon atoms or such radical in which one or more hydrogen atoms is or are replaced by hydroxy groups, etherified or esterified hydroxy groups, and/or double-bonded oxygen atoms, and

R_{10} represents hydrogen or a hydroxy or etherified or esterified hydroxy group, R_9 and R_{10} being not both hydrogen, or

R_9 and R_{10} together represents a keto group and

R_{11} represents hydrogen or a hydroxy or etherified or esterified hydroxy group.

2. A compound as claimed in Claim 1 wherein R_9 represents a saturated or unsaturated alkyl group having one to three carbon atoms or such group in which one or more hydrogen atoms is or are replaced by one or more hydroxy groups or etherified or esterified hydroxy groups and/or double-bonded oxygen atoms.

3. A compound as claimed in Claim 2, wherein R_9 represents an acetyl group.

4. A compound as claimed in Claim 2, wherein R_9 represents a hydroxyacetyl group or such group in which the hydroxy group is etherified or esterified.

5. A compound as claimed in Claim 2, wherein R_9 represents a methyl, ethyl, vinyl or ethinyl group.

6. A compound as claimed in any one of Claims 1, 2 and 5, wherein R_{10} represents a 17β-hydroxy group or such group esterified with an aliphatic carboxylic acid radical containing from one to eight carbon atoms or with an aromatic carboxylic acid radical and, R_9 represents a saturated or unsaturated hydrocarbon radical having from one to six carbon atoms in the 17α position.

7. A compound as claimed in Claim 6 having a 17β-hydroxyl group and/or a 3-hydroxy group esterified with a pentane carboxylic acid or other aliphatic carboxylic acid containing from five to eight carbon atoms.

8. A compound as claimed in Claim 6 or Claim 7, wherein R_9 represents a 17α-hydrocarbon radical being a $-C\equiv CH$, $-CH=CH_2$, $-CH_2-CH_3$, $-C\equiv C-CH_3$, $-CH=CH-CH_3$ or $-CH_2-CH_2-CH_3$ group.

9. A compound as claimed in any one preceding claim, wherein R_1, R_{32}, R_3, R_4, R_7 and R_{11} represent hydrogen and R_2 represents no double bonds or one or more double bonds at one or more of positions 1, 3, 4, 5 and 6.

10. A compound as claimed in any one of Claims 1 to 8, wherein R_5, R_6 and/or R_7 represent each a fluorine or a chlorine atom.

11. A compound as claimed in any one of Claims 1 to 10, wherein R_2 represents one or more double bonds at one or more of positions 1, 4, 5 and 3, R_3 representing an etherified or esterified hydroxy group when R_2 represents or includes a Δ^3-double bond.

12. A compound as claimed in any one of Claims 1 to 11, wherein R_2 represents two double bonds at positions 1 and 4.

13. A compound as claimed in any one of Claims 1 to 10, wherein R_2 represents two double bonds at positions 4 and 6.

14. A compound as claimed in any one of pound of Formula Y_2 in which R_2 represents double bonds at positions 3 and 5 and R_3 represents an etherified or esterified hydroxy group.

15. A compound as claimed in any one of Claims 1 to 10, wherein R_2 represents three double bonds at positions 1, 4 and 6 or positions 1, 3 and 5, R_3 representing an etherified or esterified hydroxy group when a Δ^3 double bond is present.

16. A compound as claimed in any one of Claims 1 to 9, wherein R_2 represents no double bonds and R_3 a keto group.

17. A compound as claimed in any one of Claims 1 to 11, wherein R_2 represents one double bond at position 4 and R_3 a keto group.

18. A compound as claimed in any one of Claims 1 to 11, wherein R_2 represents one double bond at position 4 and R_3 represents a hydroxy group.

19. A compound as claimed in Claim 12 or Claim 13, wherein R_1 represents a keto group.

20. A compound as claimed in any one of Claims 1 to 13, 15 to 17 and 19, being a compound of Formula T_3, wherein R_1 to R_2 and R_3 to R_{11} have the significance aforesaid and Alk represents a methyl or ethyl group.

21. A compound as claimed in any one of Claims 1 to 12 and 15, being a compound of Formula S_2 in which R_2 represents, besides the Δ^1 double bond, no other double bonds or one or more double bonds at one or more of positions 4, 5, 6, 15 and 16.

22. A compound as claimed in any one of Claims 1 to 10, 13, and 15, being a compound of Formula Y_2 in which R_2 represents besides the Δ^1 and Δ^6 double bonds, no other double bonds or one or more double bonds at one or more of positions 1, 15 and 16 R_3 and R_6 not being halogen atoms.

23. A compound as claimed in any one of Claims 1, 2 and 4 or any one of Claims 9 to 19 as appendant thereto, being a compound of Formula Z_2 in which R_{12} represents a hydroxy or etherified or esterified hydroxy group.

24. A compound as claimed in any one of Claims 1 to 6 and 8 to 23, wherein any hydroxy group present is etherified with a lower aliphatic alcohol having from one to six carbon atoms, or with a mixed aliphatic aromatic alcohol.

25. A compound as claimed in any one of Claims 1 to 6 and 8 to 23, wherein any hydroxy group present is esterified with a saturated or unsaturated monobasic or dibasic aliphatic or aromatic carboxylic acid.

26. Lumiprogesterone, being the compound of Formula VIII.

27. Δ^6-dehydro-lumiprogesterone, being the compound of Formula XXVIII.

28. 17-α-hydroxy-lumiprogesterone, being the compound of Formula XXXIII.

29. A 17-acylate of the compound claimed in Claim 28.

30. The 17-acetate of 17-α-hydroxy-lumiprogesterone, being the compound of Formula XXXV.

31. The 17-caproate of 17-α-hydroxy-lumiprogesterone, being the compound of Formula XXXVI.

32. Δ^6 - dehydro - 17α - hydroxy - lumi - progesterone, being the compound of Formula XXXVII.

33. A 17-acylate of the compound claimed in Claim 32.

34. The 17-acetate of Δ^6-dehydro-17α-lumiprogesterone, being the compound of Formula XXXVIII.

35. Lumidesoxycorticosterone 21 - acetate, being the compound of Formula XI.

36. 21 - acylate of lumidesoxycorticosterone.

37. Lumitestosterone, being the compound of Formula XVIII.

38. A 17-acylate of the compound claimed in Claim 37.

39. Lumitestosterone - 17β - (β - phenyl - propionate), being the compound of Formula XIX.

40. Δ^6 - dehydrolumitestosterone, being the compound of Formula XX.

41. A 17-acylate of the compound claimed in Claim 40.

42. Δ^6 - dehydrolumitestosterone - 17β - propionate, being the compound of Formula XXI.

43. 17α - ethinyl - lumitestosterone, being the compound of Formula XXII.

44. Δ^1 - dehydrolumitestosterone, being the compound of Formula XXIV.

45. 2 - methyl - lumitestosterone, being the compound of Formula XXVI.

46. Lumiandrost - 4 ene - 3, 17 - dione, being the compound of Formula XVI.

47. Lumiandrost - 4 - ene - 3, 17β - diol, being the compound of Formula XVII.

48. $\Delta^{4,6}$ - lumiandrostadiene - 3, 17 - dione, being the compound of Formula XLII.

49. The 3, 17α - diacetoxy - 20 - keto - $\Delta^{2,3}$-lumipregnadiene, being the compound of Formula XXXIV.

50. A method of preparing a compound as claimed in Claim 1 or any one of Claims 9 to 19 as appendant thereto, in the formula of which compound R_9 and R_{10} together represent a keto-group, which method comprises oxidising a compound of Formula J by means of an oxidising agent capable of breaking the double bond subsisting therein at the 17(20)-position, in which Formula J, X represents a bivalent residue as shown in the accompanying drawings having resultantly the same substituents and double bond structure as the compound produced being a compound of Formula K, and Q^{VI} represents a methyl group and Q^{VII} represents an aldehyde group or a cyanhydrin or bisulphite addition product derived therefrom or an O-acyl group, or Q^{VI} represents hydrogen and Q^{VII} represents a —COOR group in which R represents an aliphatic hydrocarbon radical containing from one to six carbon atoms.

51. A method of preparing a compound as claimed in Claim 1 or any one of Claims 9 to 19 as appendant thereto, in the formula of which compound R_9 represents hydrogen and R_{10} a hydroxy group or etherified or esterified hydroxy group, which method comprises reducing a compound of Formula K by means of a reducing agent, capable of reducing ketones to corresponding secondary alcohols, in which Formula K. X represents a bivalent residue as shown in the accompanying drawings having resultantly the same substituents and double bond structure as the compound produced being a compound of formula L wherein R_9 and R_{10} have the significance aforesaid.

52. A method of preparing a compound as

claimed in any one of Claims 1, 2 and 5 to 8 or in any one of Claims 9 to 19 as appendant thereto, in which compound R_9 represents a saturated or unsaturated hydrocarbon radical containing from one to six carbon atoms and R_{10} represents a hydroxy or etherified or esterified hydroxy group, which method comprises reacting a compound of Formula K with a metal acetylide, a Grignard reagent, or equivalent organometallic compound capable of reacting with a keto-group, in which Formula K, X represents a bivalent residue as shown in the accompanying drawings having resultantly the same substituents and double bond structure as the compound produced being a compound of Formula L wherein R_9 and R_{10} have the significance aforesaid.

53. A method of preparing a compound as claimed in any one of Claims 1 and 3 or any one of Claims 9 to 19 as appendant thereto in which compound R_9 represents an acetyl group and R_{10} hydrogen, which method comprises oxidising a compound of Formula D by means of an oxidising agent capable of breaking the double bond subsisting therein at the 20 (22) - position, in which Formula D, X represents a bivalent residue *as shown* in the accompanying drawings having one 17-hydrogen atom and resultantly the same other substituents and double bond structure as the compound produced being a compound of Formula E, and Q^V is hydrogen and Q^{IV} a secondary amine residue, and O-acyl group, or a C_1 to C_6 alkyl or phenyl group, or Q^{IV} and Q^V each represent such alkyl or phenyl group.

54. A method of preparing a compound as claimed in Claim 1 or Claim 4 or any one of Claims 9 to 19 as appendant thereto in the formula of which compound R_9 represents a hydroxyacetyl group or an etherified or esterified hydroxyacetyl group and R_{10} represents hydrogen, a hydroxy group, or an etherified or esterified hydroxy group, which method comprises acylating a compound of Formula Z_2 wherein R_1 to R_{11}, R_{10} and R_{11} have resultantly the same significance and Hlg represents a halogen atom, by reaction under anhydrous conditions with an alkali metal salt or alkaline earth metal salt of an organic carboxylic acid, followed if required by saponification and then if required etherification of the resulting free 21-hydroxy group.

55. A method of preparing a compound as claimed in Claim 1 or Claim 3, or any one of Claims 9 to 19 as appendant thereto, in the formula of which compound R_9 represents an acetyl group and R_{10} a hydroxyl group which method comprises reacting a compound of formula J with a per-acid and hydrolysing the resulting epoxy compound of Formula M to obtain the product aforesaid being a compound of Formula N, in which formulae J, M and N, X represents a bivalent residue as shown in the accompanying drawings having resultantly the same substituents and double bond structures, and, in Formula J, Q^{VI} represents a methyl group and Q^{VII} an aldehyde group.

56. A method of preparing a compound as claimed in Claim 21 which method comprises subjecting to selective Δ^1 - dehydrogenation a compound of Formula S_1, wherein R_2 represents no double bonds or one or more double bonds at one or more of positions 4, 5, 6, 15 and 16 and R_1, R_3, and R_5 to R_{11} have resultantly the same significance, said selective dehydrogenation being effected by direct halogenation followed by abstraction of hydrogen halide, or by selective biochemical Δ^1-dehydrogenation or by treatment with selenium dioxide or selenic acid, or with iodine pentoxide or iodic acid or substances generating the same during the reaction.

57. A method of preparing a compound as claimed in Claim 20 which method comprises subjecting a compound of formula T_1 to condensation with a dialkyl ester of oxalic acid in the presence of an alkali metal hydride or alkoxide or equivalent condensation agent, to obtain a condensation product then converted to a compound of formula T_2 wherein R_{12} represents an alkyl group being that present in the oxalate ester, and reacting said product of Formula T_2 with a methyl or ethyl halide followed by treatment with an alkali metal alkoxide, to obtain a product of Formula T_3, R_1, R_2 and R_5 to R_{10} in the formulae T_1, T_2 and T_3 having resultantly the same significances.

58. A method of preparing a compound as claimed in Claim 22 which method comprises subjecting a compound of Formula Y_1 to selective Δ^6-dehydrogenation by reaction with chloranil or by halogenating with a reagent capable of effecting halogen substitution at the allylic position in relation to the existing (Δ^4) double bond, and thereafter dehydrohalogenating in the presence of an acid binder, R_1 to R_5 and R_5 to R_{10} in formulae Y_1 and Y_2 having resultantly the same significance.

59. A method of preparing a compound as claimed in Claim 23 which method comprises subjecting a compound of Formula Z_1 to reaction with lead tetra-acetate or to microbiological hydroxylation, R_1 to R_4 and R_{11} and R_{10} in formula Z_1 having resultantly the same significance as in formula Z_2 being the formula of the product obtained, and thereafter if required etherifying or esterifying any free 21-hydroxy group formed.

60. A method as claimed in Claim 51 wherein the reduction is effected by means of a complex metal hydride, or with lithium and ammonia, or with aluminium isopropylate, or with an alkali metal and a lower aliphatic mono- or dihydric alcohol containing one to six carbon atoms.

61. A method as claimed in Claim 51 or Claim 60 which includes the step of rein-

stating a 3-keto group reduced during the reduction, by selective oxidation by means of manganese dioxide at room temperature in an anhydrous medium.

62. A method as claimed in any one of Claims 51, 60 and 61 which includes the step of esterifying the 17-hydroxy group obtained in the reduction, by means of an acid anhydride or acid halide.

63. A method as claimed in Claim 60 for preparing the compound claimed in Claim 47 wherein the compound of Formula XVI is reduced as aforesaid.

64. A method as claimed in Claim 61 for preparing the compound claimed in Claim 37, which method comprises oxidising the compound of Formula XVII as aforesaid.

65. A method as claimed in Claim 62 for preparing the compound claimed in Claim 39 wherein the compound of Formula XVIII is esterified into the 17β - (β - phenylpropionate).

66. A method as claimed in Claim 62 for preparing a compound as claimed in Claim 38 wherein the compound of Formula XVIII is esterified to the corresponding 17β-acylate.

67. A method as claimed in Claim 62 for preparing the compound claimed in Claim 42 wherein the compound of Formula XX is esterified into the 17β-propionate.

68. A method as claimed in Claim 62 for preparing a compound as claimed in Claim 41 wherein the compound of Formula XX is esterified to the corresponding 17-acylate.

69. A method as claimed in Claim 52 wherein the compound of Formula K is reacted with a saturated or unsaturated aliphatic Grignard compound containing 1 to 3 carbon atoms, the MgHlg group being not bound to an unsaturated carbon atom.

70. A method as claimed in Claim 52 wherein the compound of Formula K is reacted with an acetylide of lithium, sodium or potassium.

71. A method as claimed in any one of Claims 52, 69 and 70 wherein the compound of formula K contains a 3-keto group, which method includes protecting such group by conversion into an enamine or glycolacetal.

72. A method as claimed in Claim 52 or Claim 70 or Claim 71 wherein the compound of formula XVI is converted into the compound claimed in Claim 43.

73. A method as claimed in Claim 54 comprising condensing a compound of Formula Z_1 with a dialkyl ester of oxalic acid in the presence of an alkali metal alkoxide as condensation agent, and of a solvent, to obtain the corresponding compound of Formula Z_{1a} which is then reacted with molecular halogen to obtain, after decomposing the initial product of halogenation, the corresponding compound of Formula Z_2 which is thereafter reacted as aforesaid.

74. A method as claimed in Claim 73 wherein a 3-keto group is present in the formula Z_1 and the reaction is performed with equimolar quantities of the compound of formula Z_1 and the oxalate ester.

75. A method as claimed in Claim 73 or Claim 74 wherein the oxalate ester if dimethyl or diethyl oxalate.

76. A method as claimed in any one of Claims 73 to 75 wherein the condensation reaction is carried out at a temperature of from 15° C. to the boiling temperature of the reaction mixture.

77. A method as claimed in any one of Claims 73 to 76 wherein the halogenation is effected by means of bromine or iodine in the presence of a solvent.

78. A method as claimed in Claim 77 wherein the said solvent is an aliphatic alcohol having one to six carbon atoms.

79. A method as claimed in any one of Claims 73 to 78 wherein the halogenation is effected at a temperature of from −10 to −20° C.

80. A method as claimed in any one of Claims 54 and 73 to 79 wherein the compound of formula Z_1 is acylated by means of an anhydrous dispersion of a sodium or potassium salt of the carboxylic acid.

81. A method as claimed in any one of Claims 73 to 80 wherein lumiprogesterone is converted to 21-iodo-lumiprogesterone and thence to lumi-desoxycorticosterone acetate being the compound claimed in Claim 35.

82. A method as claimed in Claim 56 wherein the dehydrogenation is effected by reaction with selenium dioxide or selenic acid in the presence of an aqueous organic solvent.

83. A method as claimed in Claim 82 wherein the solvent is an aqueous lower (C_{1-4}) aliphatic alcohol.

84. A method as claimed in Claim 82 or Claim 83 wherein the reaction is carried out in the presence of a tertiary alcohol.

85. A method as claimed in Claim 84 wherein said tertiary alcohol is tertiary butanol or tertiary amyl alcohol.

86. A method as claimed in any one of Claims 82 to 85 wherein the reaction takes place in the presence of an organic or inorganic acid.

87. A method as claimed in Claim 86 wherein the reaction is carried out in the presence of an aliphatic carboxylic acid or a benzoic acid.

88. A method as claimed in any one of Claims 56 and 82 to 87 wherein lumitestosterone is converted into Δ^1 - dehydrolumi - testosterone being the compound claimed in Claim 44.

89. A method as claimed in Claim 57 wherein the condensation is carried out in the presence of a lower aliphatic alcohol or an aliphatic or aromatic hydrocarbon as solvent.

90. A method as claimed in Claim 57 or Claim 89 wherein the condensation product

initially formed is converted into the compound of Formula T_2 by treatment with acid.

91. A method as claimed in any one of Claims 57, 89 and 90 wherein the oxalic acid ester is dimethyl or diethyl oxalate.

92. A method as claimed in any one of Claims 57 and 89 to 91 wherein the compound of Formula T_2 is reacted with methyl or ethyl bromide or iodide in the presence of an alkali metal carbonate or bicarbonate as condensation agent.

93. A method as claimed in Claim 92 wherein the reaction is carried out at a temperature betwen room temperature and the boiling temperature of the reaction mixture for a time ranging from half an hour to forty-five hours.

94. A method as claimed in any one of Claims 57 and 90 to 93 wherein lumitestosterone is converted in to 2-methyl lumitestosterone being the compound claimed in Claim 45.

95. A method as claimed in Claim 58 which method comprises brominating the compound of Formula Y_1 by means of N-bromsuccinimide.

96. A method as claimed in Claim 58 or Claim 95 wherein the halogenation product is dehydrohalogenated by means of an organic or inorganic base.

97. A method as claimed in Claim 96 wherein the base is a tertiary amine.

98. A method as claimed in Claim 96 wherein the base is calcium oxide or calcium carbonate.

99. A method as claimed in Claim 58 which method comprises reacting the compound of Formula Y_1 with chloranil in the presence of an aromatic or aliphatic hydrocarbon or a lower aliphatic alcohol containing one to six carbon atoms, as solvent.

100. A method as claimed in Claim 58 or Claim 99 wherein the compound of Formula Y_1 is reacted with chloranil in the presence of a solvent having a boiling point exceeding 80° C.

101. A method as claimed in Claim 100 wherein the reaction is conducted at a temperature of from 100 to 150° C.

102. A method as claimed in any one of Claims 58 and 95 to 101 wherein lumitestosterone is converted into Δ^6 - dehydrolumi - testosterone being the compound claimed in Claim 40.

103. A method as claimed in any one of Claims 58 and 95 to 101 wherein lumiprogesterone is converted into Δ^6 - dehydro-lumiprogesterone being the compound claimed in Claim 27.

104. A method as claimed in any one of Claims 58 and 95 to 101 wherein 17α - hydroxy-lumiprogesterone is converted into Δ^6-dehydro - 17α - hydroxy-lumiprogesterone as claimed in Claim 32.

105. A method as claimed in any one of Claims 58 and 95 to 101 wherein a 17α - acyloxy-lumiprogesterone is converted into the corresponding Δ^6 - dehydro - 17α - acyloxy - lumiprogesterone, being a compound as claimed in Claim 33.

106. A method as claimed in any one of Claims 58 and 95 to 101 wherein 17α - acetoxy-lumiprogesterone is converted into Δ^6 - dehydro - 17α - acetoxy-lumiprogesterone as claimed in Claim 34.

107. A method as claimed in Claim 55 wherein the compound of Formula J is reacted with permonophthalic acid, peracetic acid, or perbenzoic acid.

108. A method as claimed in Claim 55 or Claim 107, wherein the reaction with the per-acid is conducted at a temperature of from C to 40° C.

109. A method as claimed in any one of Claims 55, 107 and 108 wherein, after decomposition of any excess per-acid, the epoxy compound of Formula M is hydrolysed in an alkaline or in an acidic medium.

110. A method as claimed in any one of Claims 55 and 107 to 109 which includes the step of esterifying the 17 - hydroxy - group in the compound of Formula N obtained by reaction at a temperature of from 10 to 30° C. with an excess, for example thirty equivalents, of the acid chloride or anhydride of the desired acid.

111. A method as claimed in any one of Claims 55 and 107 to 109 which includes the step of esterifying the compound of Formula N, produced, to obtain the corresponding 3-enol, 17-diester by reaction with a large excess, for example at least one hundred equivalents, of the acid chloride or anhydride of the desired acid, for a prolonged time, for example from 10 to 30 hours.

112. A method as claimed in any one of Claims 55 and 107 to 109 wherein the compound claimed in Claim 28 is obtained from the compound of Formula XIV.

113. A method as claimed in Claim 110 wherein the compound claimed in Claim 30 is obtained by esterification as aforesaid of 17α-hydroxy-lumiprogesterone.

114. A method as claimed in Claim 110 wherein the compound claimed in Claim 31 is obtained by esterification of 17α - hydroxy-lumiprogesterone as aforesaid.

115. A method as claimed in Claim 110 wherein the compound claimed in Claim 34 is obtained by esterification as aforesaid of Δ^6 - dehydro - 17α - hydroxy-lumiprogesterone.

116. A method as claimed in Claim 111 wherein the compound claimed in Claim 49 is obtained by esterification as aforesaid of 17α - hydrolumiprogesterone.

117. A method as claimed in Claim 55 or any one of Claims 107 to 116, or Claim 56 or any one of Claims 51, 52, and 60 to 72, which method comprises dehydrobrominating a compound of Formula G wherein the residue

X has resultantly the same substituents and double bond structure as in the final product, the dehydrobromination being effected with the aid of a basically-reacting inorganic or organic compound, and yielding a product of Formula J wherein Q^{VI} represents a methyl group and Q^{VII} an aldehyde group, and thereafter reacting said compound of Formula J or the cyanhydrin or bisulphite addition compound thereof, as aforesaid to produce a product of Formula N or of Formula K or of Formula L therefrom.

118. A method as claimed in Claim 117 wherein the dehydrobromination is effected by means of a metal oxide or hydroxide such as calcium or barium oxide or hydroxide or magnesium oxide, or by means of a tertiary organic nitrogen base, or, except a 3-keto group be present, by means of a primary or secondary organic nitrogen base.

119. A method as claimed in Claim 118 wherein the dehydrobromination is effected by means of pyridine.

120. A method as claimed in Claim 117 or any one of Claims 118 and 119, which method comprises adding bromine to an enamine of Formula D to obtain a compound of Formula F, hydrolysing the latter to obtain a compound of Formula G, and thereafter further reacting the latter as aforesaid.

121. A method as claimed in any one of Claims 117 to 119 which method comprises brominating a compound of Formula C being an aldehyde, by means of elemental bromine, to obtain a compound of Formula G which is thereafter reacted as aforesaid.

122. A method as claimed in Claim 121 wherein the bromination is effected under exposure to light catalytically accelerating the reaction.

123. A method as claimed in Claim 121 or Claim 122 wherein the bromination is effected in the presence of an HBr-acceptor.

124. A method as claimed in any one of Claims 121 to 123 wherein the bromination is carried out at a temperature of from 20 to 30° C.

125. A method as claimed in any one of Claims 121 to 124 wherein the bromination is carried out with exclusion of oxygen.

126. A method as claimed in Claim 120 wherein the bromination of the enamine of Formula D is carried out at a temperature of from −55 to 0° C.

127. A method as claimed in Claim 120 or Claim 126 wherein the compound of Formula F is hydrolysed by dissolving in an organic solvent, diluting with water, and maintaining at a temperature of from 10 to 30° C. for a period of from one to five hours.

128. A method as claimed in Claim 50 or any one of Claims 51, 52 and 60 to 72, which method comprises condensing a compound of Formula E with a dialkyl ester of oxalic acid by the method specified in any one of Claims 54 and 73 to 76, brominating the product obtained, and decomposing the bromination product in an alkali medium to obtain a compound of formula J, and thereafter reacting the latter as aforesaid to obtain a product of Formula K or of Formula L therefrom.

129. A method as claimed in Claim 50 or any one of Claims 51, 52, and 60 to 72, which method comprises acylating a compound of Formula B by means of isopropenyl acetate or other acylate to form an enol-acylate of Formula H, subjecting the same to catalytic double-bond shift to form the compound of Formula J, and thereafter further reacting the last as aforesaid to obtain a product of Formula K or of Formula L therefrom.

130. A method as claimed in Claim 129 wherein the acylation is effected in the presence of concentrated sulphuric acid as catalyst.

131. A method as claimed in Claim 129 or Claim 130 wherein the double-bond shift is effected in the presence of *p*-toluene sulphonic acid as catalyst.

132. A method as claimed in Claim 131 wherein the said catalyst is present in solution in acetic anhydride.

133. A method as claimed in any one of Claims 129 to 132 wherein the compound of formula E contains an enolisable system comprising a 3-keto group in combination with a double bond or bonds at positions 1 or 4 or positions 4 and 6, or other enolisable group in Ring A, which method includes the step of reconverting the enolisation effected at such group to the original group by iodinating the enolisation product with iodosuccinimide in a solvent, and thereafter diodinating with sodium bisulphite.

134. A method as claimed in Claim 53 or Claim 120 or any succeeding claim appendant thereto, which method comprises reacting a compound of Formula C being an aldyehyde, Q^{III} representing hydrogen, with a secondary amine with elimination of water to form an enamine of Formula D in which Q^{IV} represents a secondary amine residue and Q^{V} represents hydrogen, and thereafter further reacting the said enamine as aforesaid, X having the same resultant significance in the formulae C and D and the final product.

135. A method as claimed in Claim 134 wherein the reaction with the secondary amine takes place at a temperature of from 25 to 150° C.

136. A method as claimed in Claim 134 or Claim 135 wherein the reaction with the secondary amine is conducted in the presence of a solvent capable of removing water by azeotropic distillation.

137. A method as claimed in any one of Claims 134 to 136 wherein the compound of Formula C contains a 3-keto-Δ^4-system and the reaction is conducted with equimolar quantities of said compound and the amine.

138. A method as claimed in any one of

Claims 134 to 137 wherein the amine is a dialkyl- or dialkanolamine having from one to six carbon atoms in each hydrocarbon radical.

139. A method as claimed in any one of Claims 134 to 137 wherein the amine is a saturated cyclic secondary amine.

140. A method as claimed in Claim 139 wherein the amine is piperidine.

141. A method as claimed in any one of Claims 134 to 140 wherein the reaction with the amine is carried out at a temperature of from 40 to 110° C.

142. A method as claimed in Claim 53 or any one succeeding claim appendant thereto which method comprises reacting a compound of formula C being an aldehyde, Q^{III} representing hydrogen, with a carboxylic acid halide or anhydride with elimination of water in the presence of an alkali metal salt of the same acid, or of pyridine, to form an enol-acylate of Formula D, and thereafter further reacting the latter as aforesaid, X having resultantly the same significance in the formulae C and D and of the final product.

143. A method as claimed in Claim 142 wherein the said compound of formula C is reacted with acetic anhydride in the presence of sodium acetate.

144. A method as claimed in Claim 142 or Claim 143 wherein the reaction is conducted at a temperature of from 30 to 110° C.

145. A method as claimed in Claim 53 or any succeeding claim appendent thereto, which method comprises reacting an aldehyde of Formula C, Q^{III} representing hydrogen, with a phenyl or alkyl Grignard reagent to obtain a compound of formula D wherein Q^{IV} represents such phenyl or alkyl group and Q^{V} hydrogen, and thereafter further reacting the compound of formula D produced, as aforesaid.

146. A method as claimed in Claim 145 wherein the compound of Formula C is reacted with an alkyl Grignard reagent containing from one to six carbon atoms.

147. A method as claimed in Claim 145 or Claim 146 wherein the intermediately-formed —OMgX compound (X being halogen) is decomposed in a neutral or weakly acidic, preferably aqueous, medium.

148. A method as claimed in Claim 53 or any succeeding claim appendant thereto which method comprises reacting a compound of Formula C being an ester, Q^{III} representing an alkoxyl group containing one to six carbon atoms, with a phenyl or alkyl Grignard reagent, decomposing the intermediate Grignard addition product, dehydrating the resulting hydroxy compound to form a compound of Formula D wherein Q^{IV} and Q^{V} both represent phenyl or alkyl groups, and thereafter reacting the said compound of Formula D further as aforesaid.

149. A method as claimed in Claim 148 wherein the intermediate addition product is decomposed with water or an aqueous acidic medium.

150. A method as claimed in Claim 148 or Claim 149 wherein the dehydration of the said hydroxy compound is effected by distilling to dryness, if necessary in the presence of a dehydrating agent

151. A method as claimed in Claim 53 or any one succeeding claim appendant thereto which method comprises reacting a compound of formula C being an acid halide, Q^{III} representing chlorine or bromine, with diphenylcadmium or with a zinc Grignard reagent, for example C_6H_5ZnCl, to produce an intermediate ketone, reacting the latter with a phenyl- or alkyl-magnesium Grignard reagent, decomposing the resulting Grignard addition compound in an aqueous medium, dehydrating the product to obtain a compound of formula D wherein Q^{V} and Q^{IV} each represent an alkyl or a phenyl group, and thereafter further reacting the last as aforesaid.

152. A method as claimed in any one of Claims 134 to 145 which method comprises oxidising a compound of Formula B wherein Q^{I} and Q^{II} represent lower aliphatic hydrocarbon radicals each containing one to six carbon atoms, or Q^{I} represents such radical and Q^{II} hydrogen.

153. A method as claimed in any one of Claims 50, 53 and 152 wherein the oxidation is carried out by means of chromium trioxide, sodium-, potassium-, or ammonium bichromate, or potassium permanganate.

154. A method as claimed in any one of Claims 50, 53 and 152, wherein the oxidation is effected by means of ozone to form an ozonade which is subsequently decomposed.

155. The method as claimed in Claim 154 wherein the ozonide formed is decomposed reductively by means of zinc dust in acetic acid or iron powder in sulphuric acid to form an aldehyde.

156. A method as claimed in Claim 154 wherein the ozonide formed is decomposed reductively by means of an aliphatic or aromatic aldehyde to form an aldehyde.

157. A method as claimed in any one of Claims 154 to 156 wherein the oxidation is effected at a temperature of from −100° to +30° C.

158. A method as claimed in Claim 157 wherein the oxidation temperature does not exceed +10° C.

159. A method as claimed in Claim 153 wherein the oxidation temperature is from −20 to +100° C.

160. A method as claimed in Claim 159 wherein the oxidation temperature is from −10 to +30° C.

161. A method as claimed in any one of Claims 153 and 159 and 160 wherein the oxidation is effected in an acid medium.

162. A method of preparing a compound

as claimed in Claim 1 substantially as hereinbefore described with reference to any one of the foregoing specific examples.

163. A compound as claimed in Claim 1 when produced by the method claimed in any one of Claims 50 to 162.

164. A pharmaceutical preparation comprising a compound as claimed in any one of Claims 1 to 49 and 163, mixed with or dissolved or dispersed in a solid or liquid excipient.

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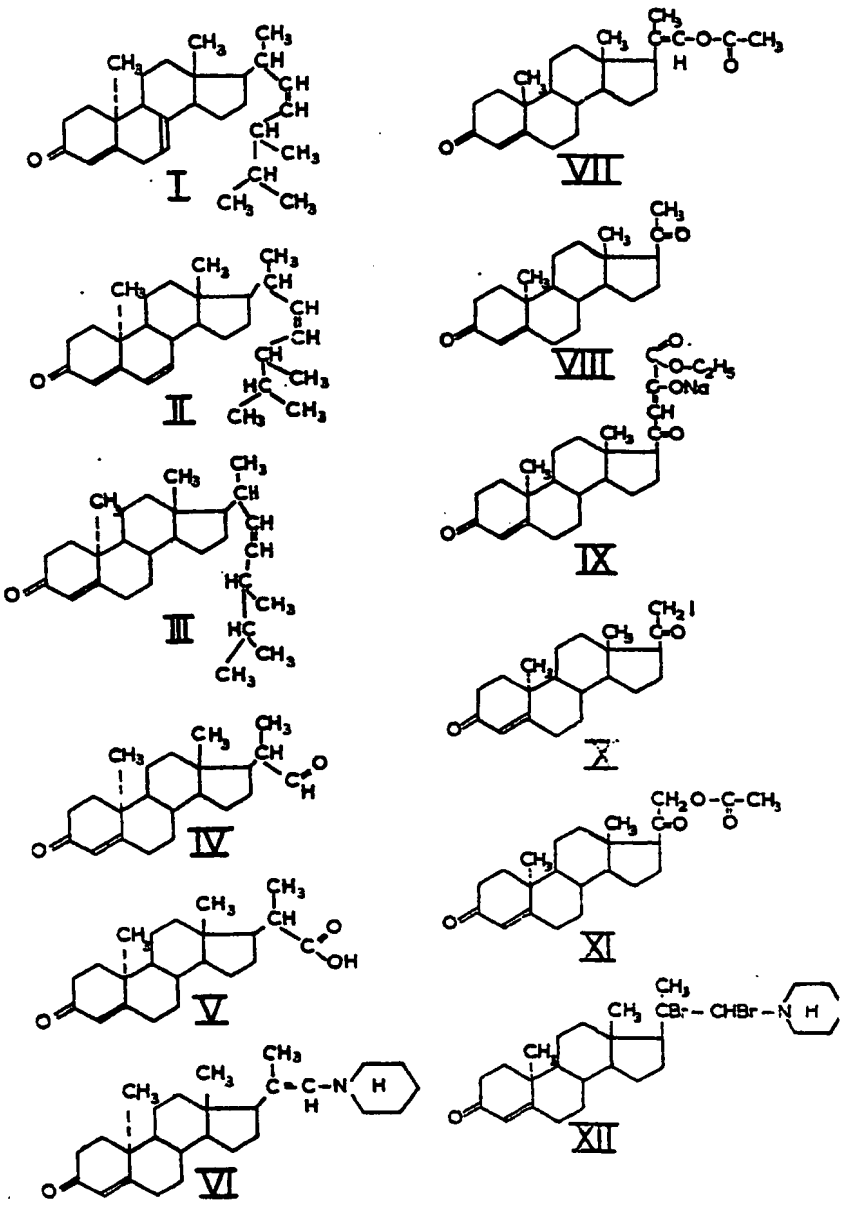

929271 COMPLETE SPECIFICATION
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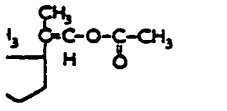
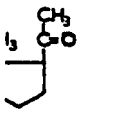
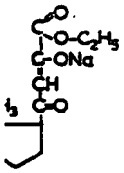
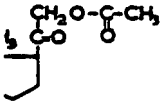
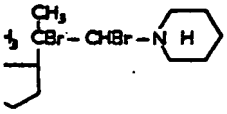
Sheets 1, 2, 3, & 4

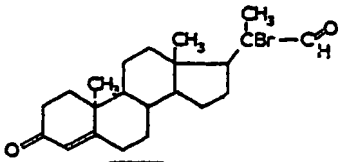












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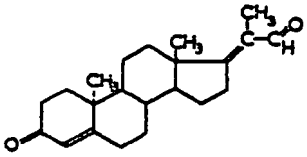

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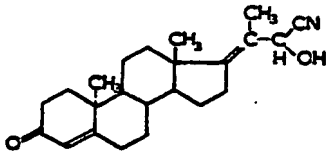

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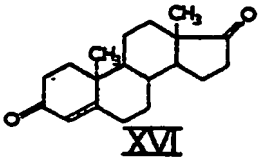

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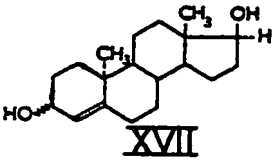

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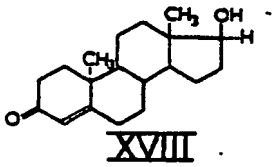

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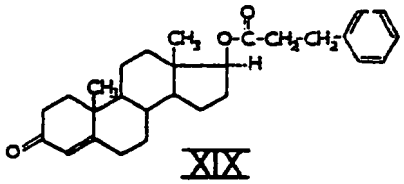

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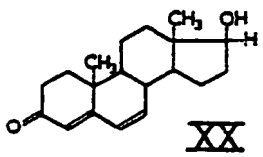

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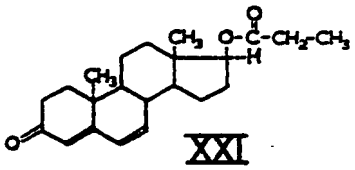

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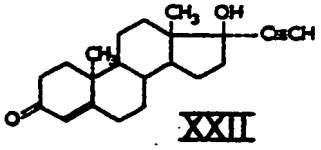

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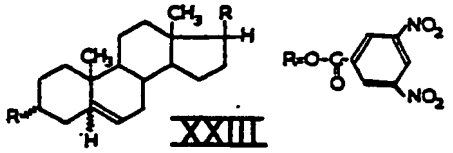

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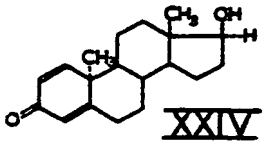

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929271 COMPLETE SPECIFICATION
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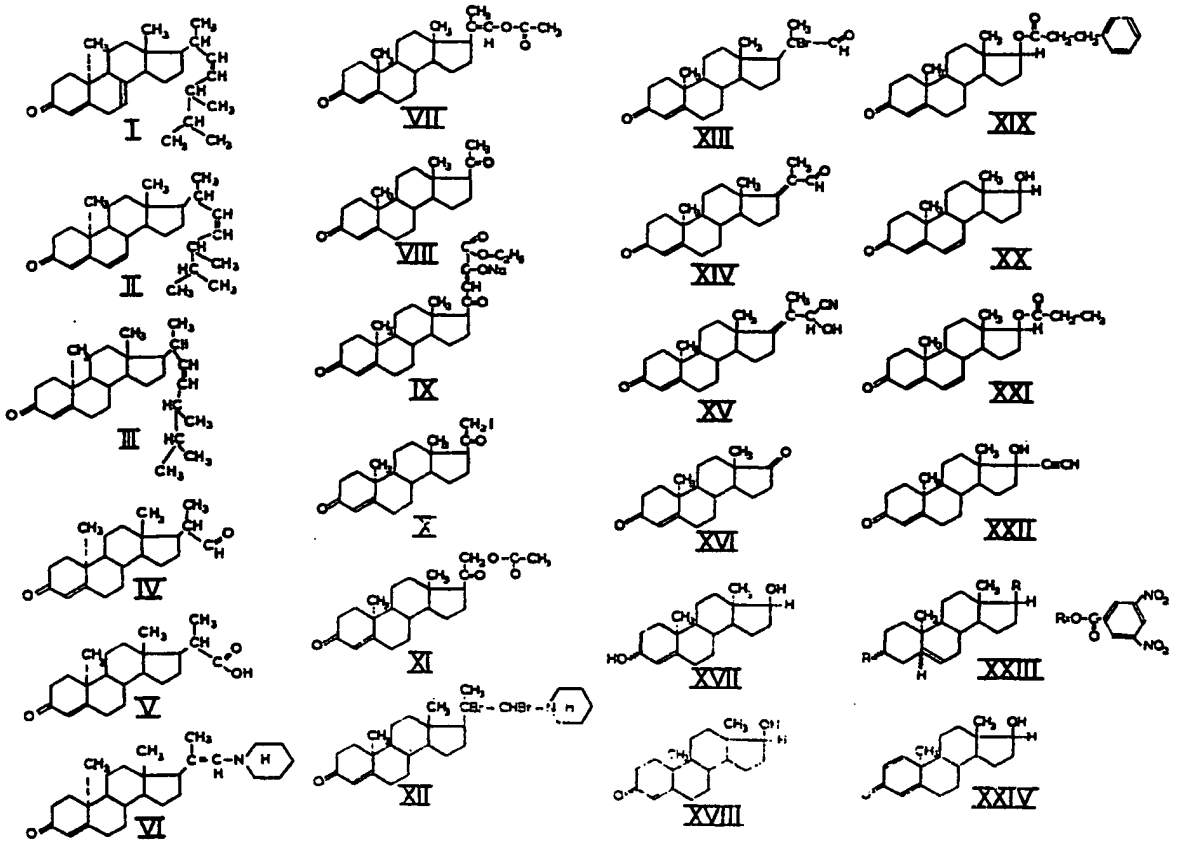

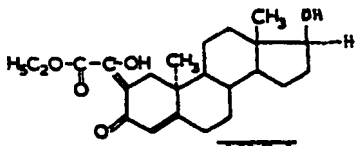

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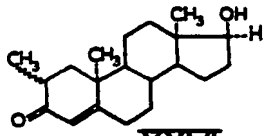

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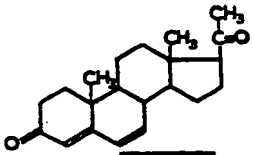

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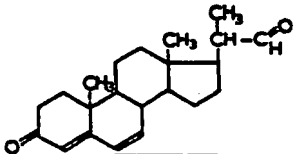

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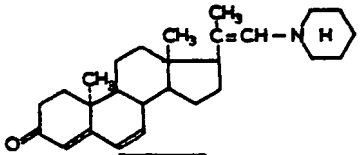

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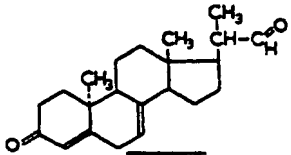

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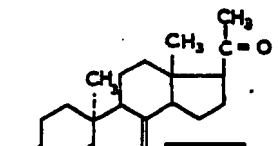

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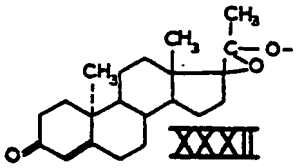

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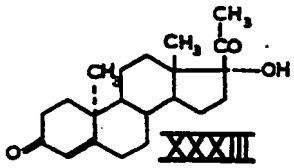

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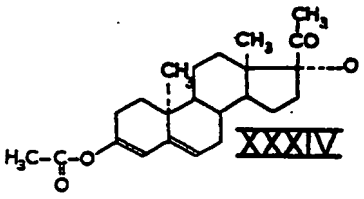

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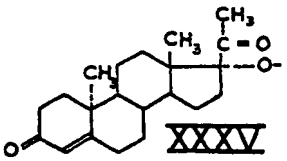

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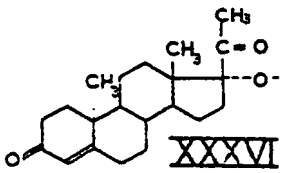

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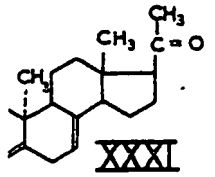

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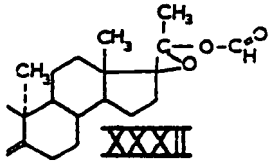

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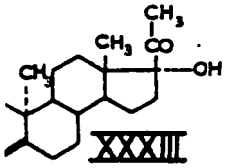

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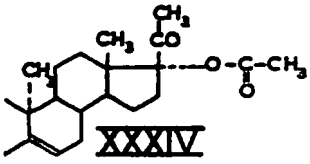

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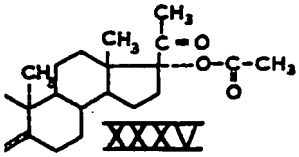

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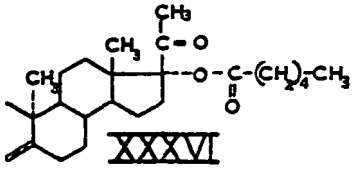

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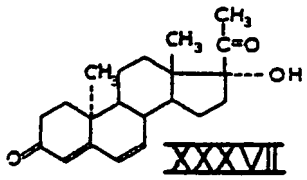

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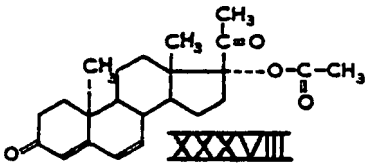

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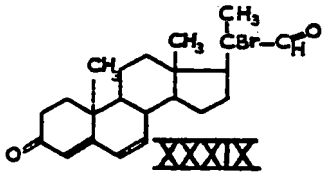

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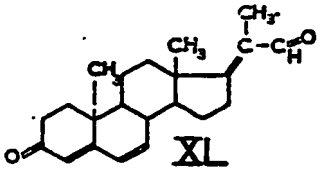

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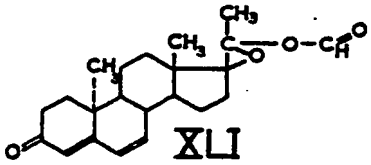

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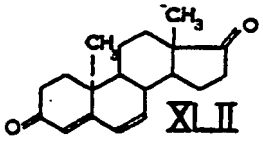

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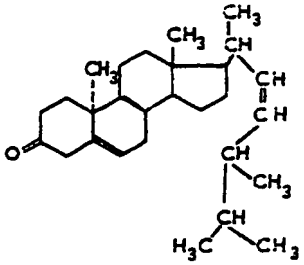

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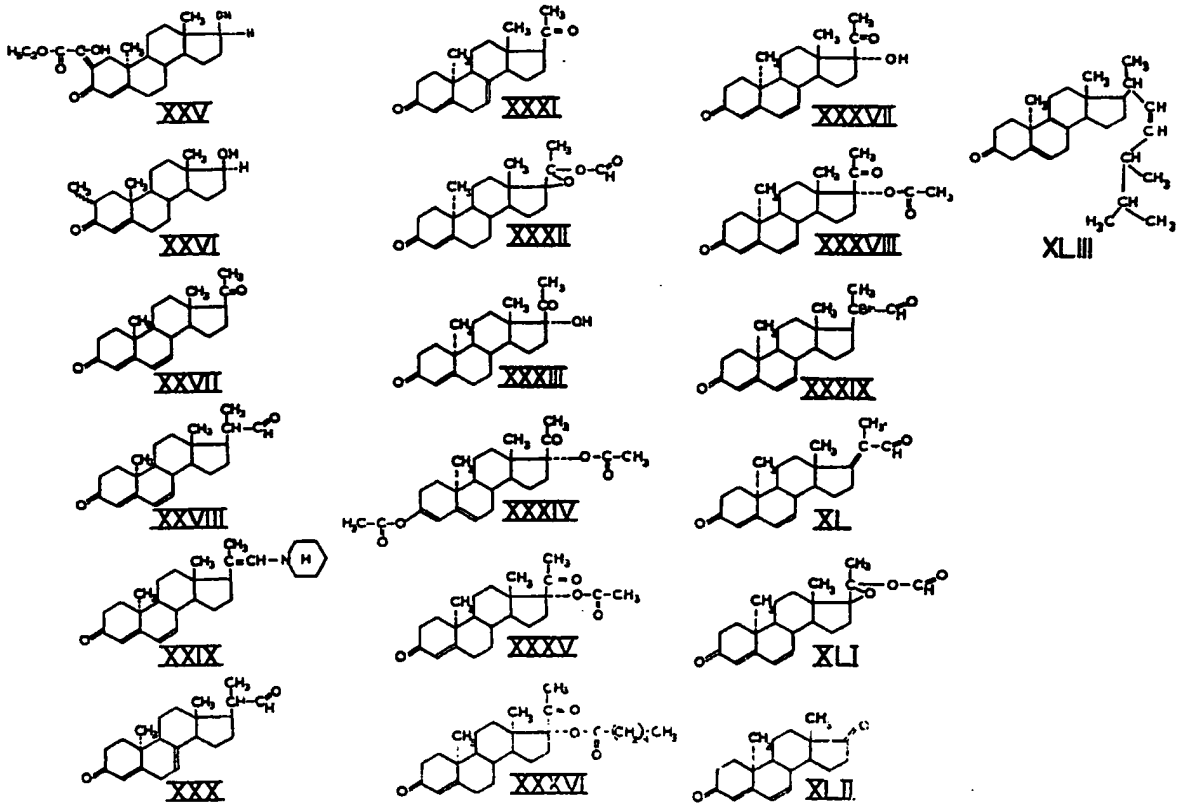

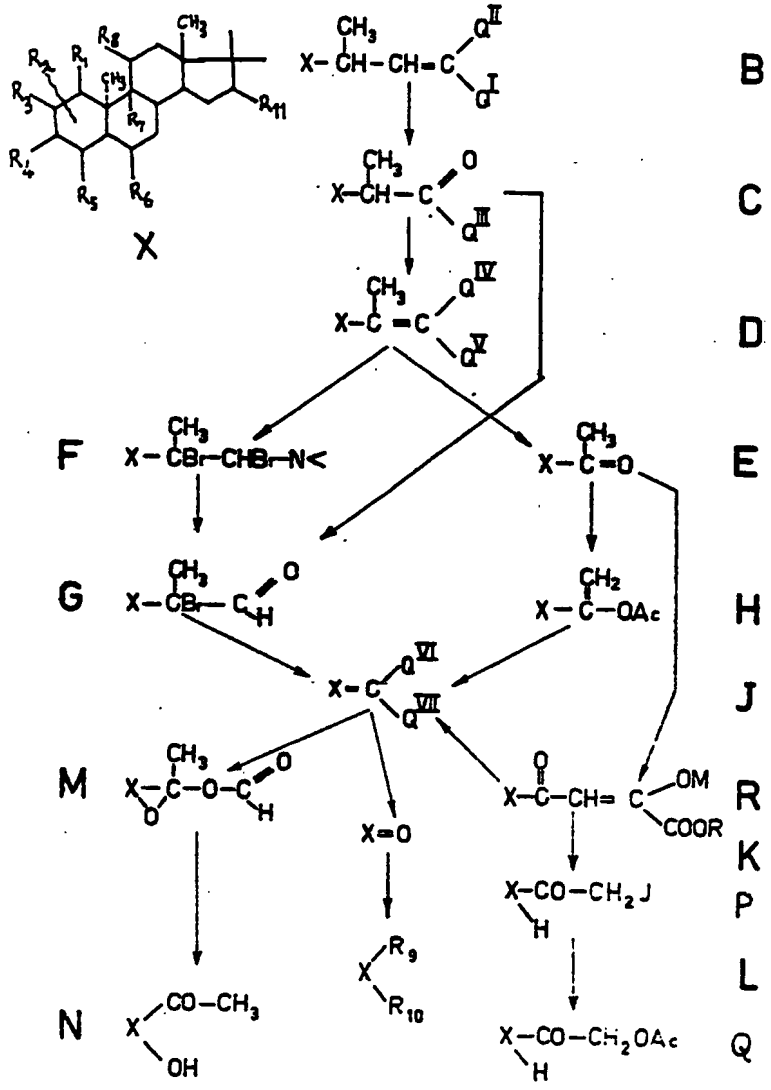
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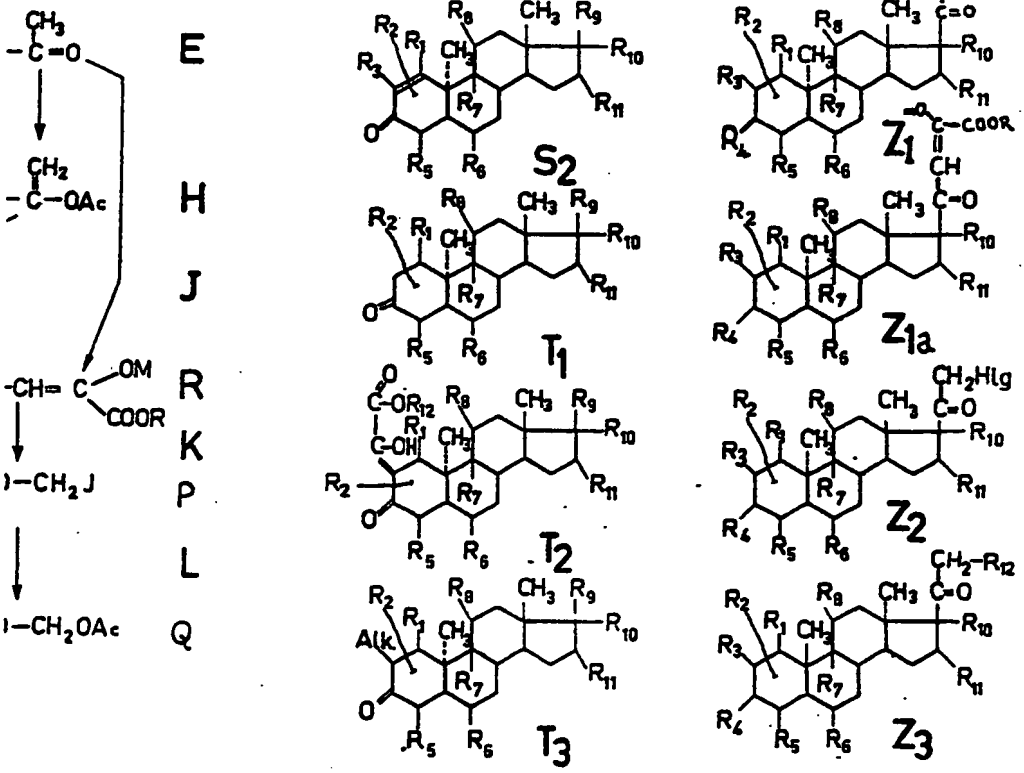
929271 COMPLETE SPECIFICATION
10 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheets 9 & 10



929271 COMPLETE SPECIFICATION
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Sheets 9 & 10